The opinion in support of the decision being entered today was ***not*** written for publication and is ***not*** binding precedent of the Board.

Paper No. 140

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

GREGORY I. GOLDBERG
Junior Party[1]
v.

KEITH E. LANGLEY, YVES A. DECLERK
and JAMES THOMAS BOONE
Junior Party[2]
v.

WILLIAM G. STETLER-STEVENSON, LANCE A. LIOTTA
and HENRY C. KRUTZSCH
Senior Party[3]

Interference No. 102,711

FINAL DECISION

Before METZ, GRON and HANLON, Administrative Patent Judges.

METZ, Administrative Patent Judge.

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[1] Application Serial Number 07/358,043, filed on May 26, 1989. Assigned to Washington University, a corporation of Missouri.

[2] Application Serial Number 07/355,027, filed on May 19, 1989. Assigned to Amgen Inc., a corporation of California.

[3] Application Serial Number 07/380,431, filed on July 17, 1989. Accorded benefit of Application Serial Number 07/326,334, filed on March 21, 1989. Assigned to the United States of America as represented by the Secretary of the Department of Health and Human Services.

The subject matter contested in this interference is directed to an isolated and purified human protein which is an inhibitor of certain enzymes and is also defined by: (1) its molecular weight; (2) its ability to form complexes with the latent form of the 72-kilodalton type IV collagenase; and, (3) the 22 (twenty-two) amino acid, N-terminal amino acid sequence of the protein. Alternatively, the purified and isolated protein is defined by its complete amino acid sequence. The particular enzyme which the protein inhibits is named a metalloproteinase. Metalloproteinases are a family of enzymes (proteins) which are naturally occurring materials and which degrade collagen. As their name suggests, the proteins defined by the count inhibit the action of the enzymes on collagen, specifically type IV collagen. Type IV collagen is a major component of basement membrane, which fills much of the space between cells in the human body. Certain tumor cells are known to secrete type IV collagenase and it is believed that type IV collagenase helps tumor cells spread throughout the body. A protein which binds with and thus inhibits type IV collagenase would, obviously, be useful in slowing the spread of tumors in the body.

The specific interfering subject matter contested by the parties is defined by the sole count in this interference, Count 3, which is set forth as follows:

COUNT 3

A purified and isolated human protein:

I) which is a tissue inhibitor of metalloproteinases, wherein:

(a) the protein has a molecular weight of from about 20 to about 28 kilodaltons;

(b) the protein forms a complex with the latent form of the 72-kilodalton type IV collagenase; and

(c) the protein has an N-terminal amino acid sequence comprising:

SPVHPQQAFCNADVVIRAKAVS; or

II) comprising the following amino acid sequence:

Cys Ser Cys Ser Pro Val His Pro Gln Gln Ala Phe Cys Asn Ala
Asp Val Val Ile Arg Ala Lys Ala Val Ser Glu Lys Glu Val Asp
Ser Gly Asn Asp Ile Tyr Gly Asn Pro Ile Lys Arg Ile Gln Tyr
Glu Ile Lys Gln Ile Lys Met Phe Lys Gly Pro Glu Lys Asp Ile
Glu Phe Ile Tyr Thr Ala Pro Ser Ser Ala Val Cys Gly Val Ser
Leu Asp Val Gly Gly Lys Lys Glu Tyr Leu Ile Ala Gly Lys Ala
Glu Gly Asp Gly Lys Met His Ile Thr Leu Cys Asp Phe Ile Val
Pro Trp Asp Thr Leu Ser Thr Thr Gln Lys Lys Ser Leu Asn His
Arg Tyr Gln Met Gly Cys Glu Cys Lys Ile Thr Arg Cys Pro Met
Ile Pro Cys Tyr Ile Ser Ser Pro Asp Glu Cys Leu Trp Met Asp
Trp Val Thr Glu Lys Asn Ile Asn Gly His Gln Ala Lys Phe Phe
Ala Cys Ile Lys Arg Ser Asp Gly Ser Cys Ala Trp Tyr Arg Gly
Ala Ala Pro Pro Lys Gln Glu Phe Leu Asp Ile Glu Asp Pro.

The claims of the parties corresponding to Count 3 are:

Goldberg: Claims 1 and 2

Langley et al.: Claims 1-4, 6, 7, 9-11,31, 32, 37 and 40-43

Stetler-Stevenson et al.: Claims 1, 9, 11 and 23-25

ISSUES

The issues presented here are priority of invention; a preliminary motion filed by Langley et al. on June 16, 2000, under 37 C.F.R. § 1.633(g), attacking the benefit accorded Stetler-Stevenson et al. of an earlier filed application, accorded when this interference was redeclared; whether Goldberg properly amended his claims designated as corresponding to the count; and, an undecided request for reconsideration filed by Langley et al. Pursuant to 37 C.F.R. § 1.640(b)[4], a decision on Langley et al.'s motion was deferred until final hearing. Because a decision on Langley et al.'s motion may effect the status of the parties and thus effect which party bears the burden of proof, we shall first decide Langley et al.'s motion attacking benefit.

THE RECORD

During the interlocutory phase of this proceeding, the parties engaged in negotiations in an attempt to reach a settlement of the issues now before us. The parties requested and were granted numerous extensions of time for the purpose of achieving a settlement agreement. During those negotiations, the parties, *inter alia*, exchanged their respective proofs of prior invention. Nevertheless,

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[4] "Unless an administrative patent judge of the Board is of the opinion that an earlier decision on a preliminary motion would materially advance the resolution of the interference, decision on a preliminary motion shall be deferred to final hearing." (emphasis added). §1.640(b) (2000).

the parties' negotiations were not successful in reaching a settlement agreement dispositive of all the issues the parties were discussing, including priority of invention. By prior agreement of the parties and by numerous orders of the administrative patent judge (APJ) handling the interlocutory phase of this proceeding, when the settlement negotiations failed the parties notified the APJ in writing of that fact and then proceeded to final hearing on priority and certain other issues based exclusively on the evidence which the parties had exchanged during their settlement negotiations. The parties have presented that evidence as the joint record of the parties. Additionally, as part of the joint record, each party has filed a volume of the exhibits referenced in their respective part of the joint record.[5]

THE MOTION UNDER 37 C.F.R. § 1.633(g)

A party seeking to change the *status quo* by filing a preliminary motion has the burden of establishing entitlement to the relief requested. The burden of proof is by the preponderance of the evidence standard. Kubota v. Shibuya, 999 F.2d 517, 520-21, 27 USPQ2d 1418, 1422 (Fed. Cir. 1993); 37 C.F.R. § 1.637(a), first sentence

[5] Reference to the joint record shall be denominated by **JR** followed by the record page number. Reference to Goldberg's exhibits shall be denominated by **GX** followed by the exhibit page number. Reference to Stetler-Stevenson et al.'s exhibits shall be denominated by **SSX** followed by the exhibit page number. Reference to Langley et al.'s exhibits shall be denominated by **LX** followed by the exhibit page number.

(1994). A preponderance of the evidence has been defined as a standard which only requires the fact finder :

> to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the [judge] of the fact's existence.

Bosies v. Benedict, 27 F.3d 539, 541-42, 30 USPQ2d 1862, 1864 (Fed. Cir. 1994), quoting from In re Winship, 397 U.S. 358, 371-72 (1970). Thus, Langley et al., as the party bringing the motion, bear the burden of proving they are entitled to the relief requested in their motion: the denial to Stetler-Stevenson et al. of the benefit accorded them of their earlier filed application, Serial Number 07/326,344.

Benefit of prior applications for priority purposes is accorded with respect to counts not claims. Daniels v. Daum, 214 USPQ 911, 917 (Bd. Pat. Int. 1982). All that is necessary for a party to be entitled to benefit of an earlier filed application for priority purposes is compliance with 35 U.S.C. § 112 with respect to at least one embodiment within the scope of the count. Hunt v. Treppschuh, 523 F.2d 1386, 1388-89, 187 USPQ 426, 429 (CCPA 1975); Den Beste v. Martin, 252 F.2d 302, 305, 116 USPQ 584, 586 (CCPA 1958); Mori v. Costain, 214 USPQ 295, 297 (BPAI 1982); MPEP § 2309.02. Thus, in order to be entitled to the relief requested by them, Langley et al. must prove that Stetler-Stevenson et al.'s earlier filed U.S. application for which they were accorded benefit does not comply with

the requirements of 35 U.S.C. § 112 with respect to at least one embodiment within the count.

Langley et al. urge in their motion that Stetler-Stevenson et al. should be denied benefit of their earlier filed application because: (1) the application does not enable, in the sense of the statute, the requirement of the count that the protein be "purified and isolated"; (2) the application does not "describe" in the sense of the statute a complex of the purified and isolated" protein with the latent form of the 72-kilodalton (kDa) type IV collagenase and would not have enabled one of ordinary skill to make such a complex; (3) the earlier filed application fails to disclose a practical utility for the "purified and isolated" protein; and, (4) there is no "written description" of the full amino acid sequence for the purified and isolated human protein set forth in the second alternative of the count and the application would not have enabled preparation of such a protein.

In their motion, Langley et al. argue that an embodiment within the first alternative of the count is not described in the benefit application because it does not disclose or describe a complex of the purified and isolated human protein with the latent form of the 72 kDa type IV collagenase. While recognizing that the benefit application broadly discloses that the purified and isolated human protein "binds with high affinity to metalloproteinase enzymes"

generally, Langley et al. urge that because at least three other type IV collagenases were known to exist at the time Stetler-Stevenson et al. filed their benefit application, it cannot be determined from the disclosure in the benefit application which of the type IV collagenases actually binds to the purified and isolated human protein disclosed in the benefit application.

Contrariwise, Stetler-Stevenson et al. argue that at the time their benefit application was filed, the cell line used to obtain the protein of interest was known to secrete, exclusively, the 72 kDa type IV collagenase (see page 13 of the opposition and the Stetler-Stevenson Declaration (IV) attached thereto and **SSX** 40). Further, Stetler-Stevenson et al. argue that because all metalloproteinase enzymes are secreted in the latent form, their benefit application necessarily describes the latent form of the 72 kDa type IV collagenase enzyme. Stetler-Stevenson et al. conclude by urging that because they were able to isolate their protein by complexing it with type IV collagenase, it would have been understood to be an inhibitor of a metalloproteinases having a molecular weight of approximately 23,000 daltons.

The major underpinning of each of Langley et al.'s reasons for why they are entitled to the relief requested is based on the ultimate allegation that Stetler-Stevenson et al.'s earlier filed application for which they were accorded benefit does not "describe"

an embodiment within either alternative of the count. Thus, except for Langley et al.'s allegation that there is no adequate disclosure of a practical utility for the protein disclosed, Langley et al.'s other stated reasons for why benefit should be denied, as the various cases interpreting the statute have held, are founded on the premise that one cannot enable subject matter which is not described.

WRITTEN DESCRIPTION

Inquiry into satisfaction of the "written description" requirement is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Satisfaction of the "written description" requirement does not require *in ipsis verbis* antecedence in the originally filed application. In re Lukach, 442 F.2d 967, 969, 169 USPQ 795, 796 (CCPA 1971). The question, therefore, is whether Stetler-Stevenson et al.'s earlier filed benefit application would have reasonably conveyed to a person of ordinary skill in the art that Stetler-Stevenson et al. invented the subject matter of the count, including all the limitations in question. In re Smythe, 480 F.2d 1376, 1382, 178 USPQ 279, 284 (CCPA 1973).

Our reviewing court has recently addressed the issue of what constitutes an adequate "written description" of an invention in an earlier application and subsequently claimed in a later filed

application in Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1323, 56 USQP2d 1481, 1483, 1486 (Fed. Cir 2000). Therein, the court reaffirmed that while satisfaction of the "written description" requirement of the statute does not require *in haec verba* support for the subject matter at issue, the disclosure must "convey with reasonable clarity to those skilled in the art that ... [the inventor] was in possession of the invention." (citations omitted). The court further explained that "[p]ut another way, one skilled in the art, reading the original disclosure, must "immediately discern the limitation at issue" in the claims." (citations omitted). The court recognized that the inquiry was factual and is decided on a case-by-case basis.

At 230 F.3d 1326-27, 56 USPQ2d 1486, the Purdue Pharma L.P. court relied heavily on the decision of one of its predecessor courts in In re Ruschig, 379 F.2d 990, 154 USQP 118 (CCPA 1967), for the proposition that:

> one cannot disclose a forest in the original application and later pick a tree out of the forest and say "here is my invention." In order to satisfy the written description requirement, the **blaze marks** directing the skilled artisan to that tree must be in the originally filed disclosure. *See id.* at 994-995, 154 USPQ at 122; *Fujikawa*, 93 F.3d at 1570-71, 39 USPQ2d at 1905; *Martin v. Mayer*, 823 F.2d 500, 505, 3 USPQ2d 1333, 1337 (Fed. Cir. 1987).

Thus, applying the court's holding to the question of whether or not a party in an interference is entitled to the benefit of an earlier filed application with respect to a count, we must consider whether or not a party's original disclosure in the application for which benefit is sought or has been accorded has "blaze marks" on specific trees that mark a trail through the forest of the party's disclosure which would have led at the time the earlier filed application was filed to subject matter defined by the count and later claimed by the party seeking benefit. See In re Ruschig, 379 F.2d 990, 994-95, 154 USPQ 118, 122 (CCPA 1967). Absent such "blaze marks", a general disclosure ordinarily will not support (describe) later claimed narrower subject matter. Fujikawa v. Wattanasin, 93 F.3d 1359, 1571, 39 USPQ 2d 1895, 1905 (Fed. Cir. 1996). The direction leading one to the later claimed narrower subject matter must be expressed in "full, clear, concise and exact" language. See Fields v. Connover, 443 F.2d 1386, 1391, 170 USPQ 276, 280 (CCPA 1971); In re Albrecht, 435 F.2d 908, 911, 168 USPQ 293, 296 (CCPA 1971); Ruschig; 379 F.2d at 996, 154 USPQ at 123.

The count in this proceeding is directed to an isolated and purified protein and is defined by two alternatives as set forth in the count as reproduced above. One alternative describes the protein of the count in terms of its molecular weight, ability to complex with a particular enzyme, and the protein's N-terminal amino acid

sequence. The second alternative defines the protein in terms of its complete amino acid sequence. Thus, the count is directed to a protein, that is, "biological material." Subsequent to the filing of the subject motion, our reviewing court has addressed satisfaction of the "written description" requirement for "biological material" in their recent decision in Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). Therein, the court found that the "written description" requirement for claims directed to "biological material" could be satisfied by the description of the functional characteristics of the "biological material" if coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. The Enzo court specifically held at 296 F.3d 1325, 63 USPQ2d at 1613 that:

> reference in the specification to a deposit in a public depository, which makes its contents available to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112, ¶ 1.

The court also considered whether the deposit by Enzo of three nucleotide sequences in the form of a recombinant DNA molecule within an *E. coli* bacterial host at the American Type Culture Collection (ATCC) constituted an adequate "written description" of those sequences when the actual sequences for the three nucleotides were, in fact, not known as of the filing date of the application in question.

The court reviewed the non-binding Guidelines issued by the Patent and Trademark Office (PTO) governing the practice within the PTO for determining satisfaction of the "written description" requirement. After their review of the guidelines, the court found that under certain conditions the "written description" requirement could be met if: (1) the genetic material claimed were described according to its functional characteristics (here, in part, the purified and isolated protein's ability to bind to the 72kDa latent form of collagenase IV); and, if (2) the structure of said genetic material was sufficiently known or disclosed. Although the motion and Stetler-Stevenson et al.'s opposition were filed before the decision in Enzo, Stetler-Stevenson et al. have argued that the process used to isolate and purify the deposited cell line, A2058 melanoma cells, and used to obtain the protein of the count satisfies the written description requirement of § 112, first paragraph. See pages 7, 8 and 11 through 14 of paper Number 122.

It is uncontested that there is no literal support in the Stetler-Stevenson et al. application for which benefit has been accorded for the limitation in the count concerning the ability of the protein to complex with the latent form of the 72 kilodalton form of type IV collagenase. Nevertheless, it is not necessary for purposes of satisfying the "written description" requirement of the first paragraph of 35 U.S.C. § 112 to have literal support for the

limitation in question in the benefit application. Rather, it is only necessary that the application in question, when read at the time of filing by the hypothetical person of ordinary skill in the art, would have conveyed to the hypothetical person of ordinary skill in the art that the subject matter of the count was "described."

According to Langley et al.'s motion, there were at least four type IV collagenases that were known at the time Stetler-Stevenson et al. filed their benefit application and which of the four collagenases actually formed the complex with the isolated and purified protein is not set forth in the benefit application. Langley et al. rely on **LX** 19; **LX** 20 and **LX** 21 as evidence that at least 4 (four) types of type IV collagenase were known to exist at the time Stetler-Stevenson et al. filed their benefit application. Stetler-Stevenson et al. respond by urging that the **A2058** human melanoma cell used as a source material was known to secrete exclusively the 72 kDa type IV collagenase under the conditions employed by Stetler-Stevenson et al. As evidence in support of their position, Stetler-Stevenson et al. rely on the declaration of William G. Stetler-Stevenson (one of the named inventors in the Stetler-Stevenson et al. involved application) and the various exhibits referenced in said declaration in support of declarant's opinions and conclusions. Specifically, Stetler-Stevenson et al. rely on, *inter alia*, **SSX** 6;

SSX 14; SSX 20; SSX 22; SSX 34; SSX 36; SSX 38; SSX 41; and SSX 42 as evidence supporting declarant's opinions and conclusions.

Thus, here, as in Enzo, Stetler-Stevenson et al.'s deposit of the melanoma cell line A2058 was incorporated by reference in the specification. See page 6 of the Stetler-Stevenson et al. specification and page 7 of Stetler-Stevenson et al.'s opposition to the motion. Here, as in Enzo, a person of ordinary skill in the art, reading the accession numbers in Stetler-Stevenson et al.'s specification, could have obtained the A2058 melanoma cell from the ATCC and purified it according to the disclosure in Stetler-Stevenson et al.'s benefit application and obtained a protein which binds to "a type IV collagenase IV." Thus, under the court's holding in Enzo the narrow question to be resolved here is whether the Stetler-Stevenson et al. disclosure can be fairly said to describe a protein which binds to the specific type IV collagenase required by the count, that is, the latent, 72 kDA type IV collagenase, based on the deposit in the ATCC of the A2058 melanoma cell line used to prepare the protein when considered with Stetler-Stevenson et al.'s disclosure of how to obtain the protein from the melanoma cell line.

As our discussion above suggests, we are satisfied that Stetler-Stevenson et al.'s earlier filed application would have reasonably conveyed to the person of ordinary skill in the art that: Stetler-Stevenson et al. had prepared a purified and isolated human

protein (see the Stetler-Stevenson et al. benefi
page 2, lines 19 through 21; page 4, lines 19 t
lines 1 and 2; page 5, lines 20 through 24; page 6, l
5; and, page 6, lines 24 and 25) which is a tissue inhibitor of metalloproteinases (see page 5, lines 20 through 24; page 6, lines 5 through 9; and page 6, lines 24 and 25 of the Stetler-Stevenson et al. benefit application) having a molecular weight of from about 20 to 23 kilodaltons (page 7, lines 13 through 16 of Stetler-Stevenson et al.'s benefit application) and that the purified and isolated human protein had an N-terminal sequence comprising: **SPVHPQQAFCNADVVIRAKAVS** (see page 2, line 11; Figure 2, amino acids 4 through 25 of the lower row in Stetler-Stevenson et al.'s benefit application).

Here, unlike the facts in Enzo, although a person of ordinary skill could have obtained the **A2058** cell line used by Stetler-Stevenson et al. to obtain the purified and isolated protein from the deposited cell line and although the protein would have been expected to bind to "type IV" collagenases, generally, whether or not the collagenase to which the protein binds is the 72 kDa type IV collagen required by the count is not described in the benefit application. In Enzo, the disclosure in Enzo's patent, U.S. Patent Number 4,900,659, was extremely specific about how the deposited cell lines could be treated to obtain the three discrete nucleotide

sequences. Specifically, the particular restriction enzyme used to cut and isolate the nucleotide insert was specifically set forth. The Enzo disclosure also explained that the result of using the restriction enzyme was seven DNA fragments, each having a particular number of base pairs. Enzo's disclosure also explained how many base pairs were in each of the discrete nucleotides claimed and further explained how the discrete nucleotide sequences could be isolated. See Enzo, at 296 F.3d 1326, 63 USPQ 2d 1614 and column 13, lines 27 through 60 of the Enzo patent. Such specificity is lacking in Stetler-Stevenson et al.'s benefit application.

In Stetler-Stevenson et al.'s specification, specifically, at page 6, lines 2 and 3 of the Stetler-Stevenson et al. benefit application, the human melanoma cell line **A2058** is disclosed as having been deposited in the ATCC. On page 4, lines 10 and 11 of the specification, the protein is described as a glycoprotein which "specifically inhibits interstitial collagenase on a 1:1 stoichiometric basis." On page 4, under the heading "Description of Figures", it is disclosed that the protein "was purified by affinity chromatography of **A2058** human melanoma cell conditioned media on type IV collagenase-gelatin sepharose." The eluted material from that column was further purified and subsequently electrophoresed and visualized by silver staining. Stetler-Stevenson et al. thereafter recite that the inhibitor, that is, the protein, "was isolated and

purified by means described below." See page 6, lines 4 and 5. In Example 1 (page 6, line 24 through page 7, line 16), the protein of interest is described as having been purified from "the serum-free conditioned media of the human A2058 melanoma cell line." The serum-free conditioned media was collected and filter sterilized by passing through a 0.22μ filter. The conditioned media was thereafter concentrated and passed through a gelatin sepharose affinity column. The column was then eluted and the eluted fraction concentrated. After further concentration, the fraction was electrophoresed and a single band of protein identified with an apparent molecular weight of 23,000 daltons.

We find that the above-noted disclosure in the Stetler-Stevenson et al. benefit application clearly indicates that a complex of the isolated and purified human protein with a "type IV collagenase" was obtained. Langley et al. does not appear to suggest that Stetler-Stevenson et al. did not obtain a complex but only that for the complex obtained which "type IV collagenase" bound to the protein cannot be determined from Stetler-Stevenson et al.'s disclosure. Nevertheless, assuming that Langley et al. is correct and that there were only four known type IV collagenases at the time Stetler-Stevenson et al. filed their benefit application, it is reasonable to presume that the person of skill in the art would have understood it could only have been a complex with one of the four

"type IV collagenases." Thus, the even narrower question before us is whether the disclosure of forming a complex of the purified and isolated human protein with one or more of four "type IV collagenases" known by the hypothetical person of ordinary skill in the art to exist at the time Stetler-Stevenson et al. filed their benefit application is for an embodiment which satisfies the "written description" requirement of § 112, paragraph one, for the limitation in the count that the complex is with a specific "type IV collagenase, that is, the latent 72 kDa type IV collagenase.

It is apparent from the Stetler-Stevenson et al. disclosure that because the protein of interest, denominated by Stetler-Stevenson et al. as tumor cell collagenase inhibitor (TCCI), was isolated and purified by affinity chromatography on a "type IV collagenase-gelatin sepharose" (see page 4, lines 2 through 22 of the specification) that TCCI must have formed a complex with "type IV collagenase" in order to be separated from the conditioned cell media on the sepharose column. Nevertheless, the question to be resolved still remains: which type of "type IV collagenase" did Stetler-Stevenson et al. use to bind the protein of interest?

We agree with Langley et al.'s position as supported by the evidence proffered by them with their motion that at least four different "type IV collagens" were known to exist at the time Stetler-Stevenson et al. filed their benefit application. Stetler-

Stevenson et al. do not address, let alone challenge, this fact in their opposition to Langley et al.'s motion. Under the court's holdings in Purdue, supra, we find that Stetler-Stevenson et al.'s disclosure lacks the "blaze marks" which would have led a person of ordinary skill in the art to conclude that the "type IV collagen" to which their protein bound was, indeed, the latent 72 kDa type IV collagen required by the count instead of one of the three other known type IV collagenases. That it may have been obvious that the type IV collagenase could have been the latent 72 kDa type does not satisfy the written description requirement of the statute. Lockwood v. American Airlines Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Moreover, Stetler-Stevenson et al.'s proffered evidence does not support their position that the deposited cell was "known to secrete exclusively the 72 kDa type IV collagenase under the conditions employed by Stetler-Stevenson et al." as argued at page 13 of Paper Number 122. Accordingly, we find that Stetler-Stevenson et al.'s benefit application does not "describe", in the sense of the statute, an embodiment within the first alternative of the count.

In reaching the above conclusion, we have not overlooked Stetler-Stevenson et al.'s argument that in their application they distinguish the "type IV collagenase" used by them to form a complex with the protein of interest from "a poorly characterized 94 kD

gelatinase and several low molecular weight gelatinases and telopeptidases" (see page 3 of the benefit application). There is simply no adequate description of the "low molecular weight gelatinases and telopeptidases" which would have been understood by the person of ordinary skill in the art to be the other "type IV" collagenases shown by Langley et al. to have been known at the time the benefit application was filed. Indeed, the discussion at page 3 of the benefit application is not specifically directed to type IV collagenases but to matrix metalloproteinases, in general.

Because Enzo was decided after the subject motion was filed, neither party has addressed whether the Stetler-Stevenson et al. application may be found to "describe" an embodiment within the second alternative of the count under the court's holding in Enzo. Specifically, neither party has addressed whether, under the court's holding in Enzo, Stetler-Stevenson et al.'s benefit application "describes" a "purified and isolated" human protein comprising the following amino acid sequence:

Cys Ser Cys Ser Pro Val His Pro Gln Gln Ala Phe Cys Asn Ala
Asp Val Val Ile Arg Ala Lys Ala Val Ser Glu Lys Glu Val Asp
Ser Gly Asn Asp Ile Tyr Gly Asn Pro Ile Lys Arg Ile Gln Tyr
Glu Ile Lys Gln Ile Lys Met Phe Lys Gly Pro Glu Lys Asp Ile
Glu Phe Ile Tyr Thr Ala Pro Ser Ser Ala Val Cys Gly Val Ser
Leu Asp Val Gly Gly Lys Lys Glu Tyr Leu Ile Ala Gly Lys Ala
Glu Gly Asp Gly Lys Met His Ile Thr Leu Cys Asp Phe Ile Val
Pro Trp Asp Thr Leu Ser Thr Thr Gln Lys Lys Ser Leu Asn His
Arg Tyr Gln Met Gly Cys Glu Cys Lys Ile Thr Arg Cys Pro Met
Ile Pro Cys Tyr Ile Ser Ser Pro Asp Glu Cys Leu Trp Met Asp
Trp Val Thr Glu Lys Asn Ile Asn Gly His Gln Ala Lys Phe Phe

Ala Cys Ile Lys Arg Ser Asp Gly Ser Cys Ala Trp Tyr Arg Gly Ala Ala Pro Pro Lys Gln Glu Phe Leu Asp Ile Glu Asp Pro.

For reasons which follow, we find that Stetler-Stevenson et al.'s benefit application does not "describe" an embodiment within the second alternative of the count.

As we have found above, a person of ordinary skill in the art could have obtained the **A2058** cell line deposited in the ATCC and, by following the procedure outlined in Stetler-Stevenson et al.'s disclosure, obtained a protein which bound to a type IV collagenase. In their disclosure at page 7, Stetler-Stevenson et al. describe the amino acid sequencing of the protein following reduction and alkylation of said protein. The first forty amino acids of the sequence in Figure 2 is said to have been obtained after reduction and alkylation of the purified protein. The sequences obtained after treatment with an enzyme, endoproteinase, is also set forth in Figure 2 from amino acids 56 through 79; 93 through 152 and 162 through 196. According to page 5 of their specification, the bottom line in Figure 2 shows "the novel sequence of the invention obtained from direct amino acid sequencing of the protein and endoproteinase **Lys-C** peptides."

It is apparent that Figure 2 of the benefit application does not set forth the complete sequence as recited in the second alternative to the count. Further, for those sequences which are set

forth there are substantial differences in the sequence described in Figure 2 compared to the sequence required by the count. Whether a person of ordinary skill in the art, following Stetler-Stevenson et al.'s disclosure, could have obtained the sequence for the isolated and purified protein required by the second alternative of the count or would have obtained a different sequence than that set forth in Figure 2 is left to pure conjecture. Nonetheless, we are not without some discussion of this issue in the papers filed by the parties. Specifically, Langley et al. urge that there are so many errors in the sequence in Figure 2 that a person of ordinary skill in the art, possessed of the purified and isolated protein of the count, would have concluded the wrong protein had been isolated based on the reported sequence in Figure 2. See page 12 of Paper Number 120. The basis for this argument is that the alleged "correct sequence" for the protein is set forth in Langley et al.'s involved application. Thus, Langley et al. argue that Stetler-Stevenson et al.'s benefit application discloses "incomplete and inaccurate sequencing information."

Stetler-Stevenson et al.'s only response to the position advanced by Langley et al. may be found on pages 15 and 16 of Paper Number 122. Therein Stetler-Stevenson et al. set forth two arguments. First, they argue that because the partial sequence disclosed in their benefit application "confirmed homology with TIMP", the benefit

application discloses the correct sequence required by the count. Second, they argue that the amino acid sequence is merely an inherent property of the protein and need not be exemplified in order to be entitled to benefit of the earlier application. Stetler-Stevenson et al. direct our attention to two decisions, one by our reviewing court and one by the United States District Court for the District of Maine. We do not find either of these arguments to be persuasive.

Stetler-Stevenson et al.'s first argument ignores what is required by the second alternative for the count. The second alternative of the count requires the complete 194 amino acid sequence as recited in the count. Thus, we do not understand the relevance of the partial sequence disclosed in the benefit application or its "homology with TIMP", a different protein than the protein of the count, to the issue of whether the benefit application "describes", in the sense of the statute, an embodiment within the second alternative within the count. With respect to the second alternative of the count, Stetler-Stevenson et al.'s conclusion that the benefit application "discloses the correct amino acid sequence required by the Count" is unsupported by any evidence and is, indeed, manifestly erroneous.

Stetler-Stevenson et al.'s argument concerning the alleged inherency of the sequence is also not persuasive. The decision in Kennecott relied on by Stetler-Stevenson et al. was based on the fact

that the property found to be inherent in the thing claimed, a ceramic, would have been apparent on mere inspection by "anyone with a microscope." Here, the amino acid sequence of a protein is not amenable to determination by mere observation of the protein, even when viewed through a microscope. We find far more relevant to the issue before us the decision in Langer v. Kaufman, 465 F.2d 913, 915, 175 USPQ 172, 174 (CCPA 1972) cited by the court in Kennecott. As the court held in Langer, the party asserting that a property specifically recited in a count but not expressly described in the party's application bears the burden to show that the **necessary and only reasonable** interpretation to be given the application's disclosure by the hypothetical person of ordinary skill in the art supports the limitation in the count not expressly set forth in the application. This Stetler-Stevenson et al. have failed to do. The benefit application does not necessarily lead to the conclusion that the amino acid sequence of the second alternative of the count is the amino acid sequence for the protein denominated as TCCI by Stetler-Stevenson et al. in their benefit application.

Because we have found that Stetler-Stevenson et al.'s benefit application does not describe an embodiment within the count, it is unnecessary for us to reach Langley et al.'s other legal theories (non-enablement; lack of practical utility) set forth in their motion for why the relief requested should be granted.

Accordingly, for all the above reasons, the Langley et al. motion to deny Stetler-Stevenson et al. the benefit of their application Serial Number 07/326,334, filed on March 21, 1989, is GRANTED. As a result of granting the motion, Stetler-Stevenson et al.'s effective filing date is the date of their involved application, that is, July 17, 1989. Based on their effective filing date, Stetler-Stevenson et al. are now a junior party in this interference and Langley et al. are now the senior party.

GOLDBERG'S CLAIMS

In his order of March 31, 1998, the APJ, *sua sponte*, found certain claims of the parties Goldberg and Stetler-Stevenson et al. designated as corresponding to the count to be unpatentable because the claims were "understood to embrace the native protein, TIMP-2, recognized by all the parties to this interference as occurring naturally in human beings." The APJ informed the parties that his *sua sponte* finding of unpatentability could be overcome by "inserting in the claims the limiting language "isolated and purified" to further define the protein and distinguish it from the native protein." See pages 22 and 23 of Paper Number 60. After numerous requested extensions of time for, *inter alia*, responding to the APJ's *sua sponte* finding, were granted, the APJ granted a final extension of time for responding until November 12, 1999, including motions to

amend application claims under 37 C.F.R. § 1.633(c). See Paper Number 82.

On November 18, 1999 (c.o.m. November 10, 1999), Goldberg filed, *inter alia*, a response to the *sua sponte* finding (Paper Number 84) and an amendment to Goldberg's involved application (Paper Number 86). In his response to the *sua sponte* finding Goldberg proposed to amend claim 1 of his involved application in the manner suggested by the APJ. Additionally, Goldberg explained why he believed there was a basis in his as-filed disclosure for changing the language in claim 1 from "a novel protein" to --- an isolated and purified protein ---. Langley et al., within the time extended by the APJ for opposing any party's motions filed in response to the *sua sponte* finding, made several arguments explaining why the amendment should not be permitted. Langley et al. have repeated in their brief at pages 40 through 43 some of the reasons raised in their opposition to Goldberg's amendment. Langley et al. urge in their brief that "[f]or the reasons set forth in that Opposition" the proposed amendments to Goldberg's claims designated as corresponding to the count should be denied. We disagree with Langley et al.'s arguments. We find there is ample support for the proposed changes; we find that the amended claims are, indeed, enabled; and, we also find that Langley et al.'s position, as taken by them in their brief, is procedurally flawed.

It is abundantly clear from Goldberg's disclosure that the protein obtained by him was isolated and purified from the enzyme/protein complex according to the methodology specifically set forth on pages 8 through 11 of the specification of Goldberg's involved application. Moreover, it is apparent from the unconditional tenor of the APJ's suggestion to Goldberg and Stetler-Stevenson et al. ("This rejection could be overcome by inserting in the claims the limiting language "isolated and purified" to further define the protein and distinguish it from the native protein.") that the APJ believed both parties had descriptive support in their disclosures which would permit them to amend their involved claims in the manner suggested by the APJ.

Langley et al.'s argument that Goldberg's disclosure is non-enabling is founded on a mischaracterization of Goldberg's disclosure. Goldberg's disclosure does not, as Langley et al suggest, "teach that the N-terminal sequence of TIMP-2 is "SPV" (**Ser-Pro-Val**)." Rather, the sequence at page 14 of Goldberg's specification is described at page 13 of the specification as a "partial amino acid sequence of the 24-kDa protein." We find that Goldberg's disclosure, as it would have been understood by a person of ordinary skill in the art when filed, would have enabled obtaining, purifying and sequencing the protein denominated by Goldberg as TIMP-2.

More significantly, however, Langley et al., the party raising this issue, bears the burden of proving that Goldberg's disclosure is non-enabling. Under well-settled case law interpreting the enablement requirement of the first paragraph of section 112, Langley et al. have not adequately made their case against Goldberg's presumptively enabling disclosure.[6] Additionally, Langley et al.'s attempt to incorporate by reference in their brief their opposition to Goldberg's motion is improper. The rules require that it is a party's brief which must set forth the arguments and the underlying reasons in support of those arguments. Incorporating by reference an argument made in a paper other than the brief does not satisfy the rule. It is a party's brief which must set forth all the arguments a party wishes the Board to consider and it is improper to request the Board to go on a scavenger hunt, searching for papers incorporated by reference and then, after finding the paper, further searching the incorporated paper for arguments which may support the position taken by the party in the party's brief. Such burden shifting is impermissible and would place this Board in the position of being an advocate for a party's position taken in another paper unrelated to their brief.

Langley et al.'s argument that Goldberg's claims are indefinite under the second paragraph of § 112 based on the grounds

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[6] In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

the APJ found the count "unclear" ignores the differences between claims and a count. A count is given its broadest reasonable interpretation and, absent ambiguity, is interpreted without resort to any party's disclosure. Compliance with respect to the second paragraph of the statute for claims, however, is determined by first reading the claims, not in a vacuum, but in light of the supporting specification, without importing limitations from the disclosure into the claims. In re Moore, 439 F.2d 1232, 1234, 169 USPQ 236, 238 (CCPA 1971); In re Hammack, 427 F.2d 1378, 1382, 166 USPQ 204, 208 (CCPA 1970); In re Prater, 415 F.2d 1393, 1404, 1405, 162 USPQ 541, 550, 551 (CCPA 1969). It is clear from Goldberg's disclosure at page 14, line 25 through page 15, line 12, especially lines 1 through 3 of page 15, that it is the complex of the enzyme and the protein which is activated by organomercurials not the protein itself. Thus, although the claim is not a model of clarity, its meaning would have been readily understood by a person of ordinary skill in the art when read in light of Goldberg's disclosure.

Finally, Langley et al.'s argument that Goldberg "failed to file a proper Rule 633 (c)(2) motion" is founded on Langley et al.'s erroneously taken and unproved position that Goldberg's claim 1 is unpatentable under the first and second paragraphs of the statute. Langley et al. urge that because claim 1 is unpatentable Goldberg has failed to satisfy the requirements of § 1.633(c)(2) for a motion to

amend an application claim corresponding to the count, which section requires the moving party to show the patentability of each claim which the moving party proposes to amend. Rather than address the language of the entire claim 1, Langley et al. improperly focus on one limitation to the exclusion of all other claim limitations. Accordingly, Langley et al. have not satisfied their burden of persuasion.

LANGLEY ET AL.'S REQUEST FOR RECONSIDERATION

At page 43 of their brief, Langley et al. request we consider their undecided request for reconsideration filed on November 16, 1999.[7] As they did with respect to the issue of the alleged unpatentability of Goldberg's claims, rather than set forth their reasons for why the relief they request in their request for reconsideration should be granted, Langley et al. again refer this Board to another paper filed in this proceeding for the reasons why we should withdraw the APJ's dismissal of two preliminary motions and instead grant said motions. To the extent the relief requested by

[7] Although the request for reconsideration includes a certificate of service indicating the paper was served on the other parties on the due date for filing the paper, that is, November 12, 1999, the request for reconsideration was not accompanied by a certificate of mailing. While the purpose for a certificate of mailing (37 C.F.R. § 1.8) and a certificate of service (37 C.F.R. § 1.646(e)) are not co-extensive, we find no prejudice to the parties in considering the request for reconsideration as timely filed because the parties were served the paper by the date the paper was due to be filed in the PTO and we believe it would be in the interest of justice at this late date in this proceeding to consider the paper as having been timely filed.

Langley et al. is founded on arguments and reasons set forth in the paper filed in November 1999, it is denied.

Moreover, at the time the decision on motions was rendered, the rules provided that the request for reconsideration must set forth with particularity "the points believed to have been misapprehended or overlooked in rendering the decision. 37 C.F.R. § 1.640(c) (1998). In 1998, there was also a presumption that all interlocutory decisions of the APJ were correct and there was a burden on the party attacking the decision to show an abuse of discretion by the APJ in order to have the interlocutory decision overturned. 37 C.F.R. § 1.655(a). This rule was amended in 1999 and the abuse of discretion standard applies now only to procedural matters.

Abuse of discretion has been found where the decision: is clearly unreasonable, arbitrary or fanciful: is based on an erroneous conclusion of law; rests on clearly erroneous findings of fact; or, involves a record that contains no evidence on which the Board could rationally base its decision. Abrutyn v. Giovanniello, 15 F.3d 1048, 1050-51, 29 USPQ2d 1615, 1617 (Fed. Cir. 1994), citing Heat & Control, Inc. v. Hester Indus. Inc., 785 F.2d 1017, 1022, 228 USPQ2d 926, 930 (Fed. Cir. 1988).

The APJ, in his interlocutory decision below, dismissed two of Langley et al.'s preliminary motions on procedural grounds.

Specifically, the APJ dismissed the subject motions on the grounds that the motions, when filed, did not comply with 37 C.F.R. §§ 1.637(a)(1) and 1.637(a)(3). (1992). Issues raised in dismissed motions are not entitled to review on the merits. Bayles v. Elbe, 16 USPQ2d 1389, 1392 n.9 (BPAI 1990), Land v. Dreyer, 155 F.2d 383, 386, 69 USPQ 602, 605 (CCPA 1946), Jacobs v. Moriarity, 6 USPQ2d 1799, 1802 (BPAI 1988). Because the request seeks reconsideration of a dismissed motion, the standard for review under either the "old" rule or the rule as amended in 1999 is whether or not the APJ abused his discretion in dismissing the motion. Nothing in Langley et al.'s brief addresses let alone establishes any one of the four criteria for finding an abuse of discretion as set forth in the cases above. Accordingly, the request for reconsideration is **DENIED**.

PRIORITY OF INVENTION

In light of our decision granting Langley et al.'s motion to deny Stetler-Stevenson et al. the benefit of their earlier filed application, Goldberg and Stetler-Stevenson et al. are the junior parties in this interference and bear the burden of persuasion on priority of invention. 37 C.F.R. § 1.657(a). Because all the parties in this proceeding are involved based on their copending U.S. patent applications, the junior parties Goldberg and Stetler-Stevenson et al. bear the burden of establishing priority of invention by a preponderance of the evidence. 37 C.F.R. § 1.657(b). Holmwood v.

Sugavanum, 948 F.2d 1236, 1238, 20 USPQ2d 1712, 1714 (Fed. Cir. 1991); Morgan v. Hirsch, 728 F.2d 1449, 1451, 221 USPQ 193, 194 (Fed. Cir. 1984); Peeler v. Miller, 535 F.2d 647, 651 [n.5], 190 USPQ 117, 120 [n.5] (CCPA 1976).

In order to be awarded priority in this interference, one of the junior parties in this proceeding must prove either an actual reduction to practice prior to May 15, 1989, Langley et al.'s effective filing date and the date of their constructive reduction to practice, or prove a conception of the subject matter of the count before Langley et al.'s effective filing date of May 15, 1989, or any earlier date of conception proved by Langley et al., coupled with reasonable diligence just prior to Langley et al.'s date of conception, up to a reduction to practice (constructive or actual) by one of the junior parties. Jepson v. Egly, 231 F.2d 947, 957, 109 USPQ 354, 362 (CCPA 1956); Hull v. Davenport, 90 F.2d 103, 105, 33 USPQ 506, 508 (CCPA 1937); Wilson v. Sherts, 81 F.2d 755, 762, 28 USPQ 379, 383 (CCPA 1936). Assuming that one of the junior parties satisfies their burden of persuasion and proves a date of priority prior to the senior party's effective filling date, then we must then consider the senior party's evidence of priority of invention.[8]

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[8] Rule 301 of The Federal Rules of Evidence, "**Presumptions in General in Civil Actions and Proceedings**" recites: "In all civil actions and proceedings not otherwise provided for by Act of Congress or by these rules, a presumption imposes on the party against whom it is directed the burden of going forward with evidence to rebut or meet the presumption, but does not shift to such party the burden of proof in the sense of the risk of nonpersuasion, which remains throughout the

THE COUNT

It is by now well-settled that, absent ambiguity, a count in an interference is to be given the broadest, reasonable interpretation that the language of the count permits without resort to either party's disclosure. DeGeorge v. Bernier, 768 F.2d 1318, 1321-22, 226 USPQ 758, 761 (Fed. Cir. 1985); Fontijn v. Okamoto, 518 F.2d 610, 617, 186 USPQ 97, 102-3 (CCPA 1975); Lamont v. Berguer, 7 USPQ2d 1580, 1582 (BPAI 1988). Here the count is expressed in two alternative forms. The first alternative describes a "purified and isolated" human protein defined by four specific characteristics. The term "purified and isolated" was *sua sponte* added to the count proposed by the APJ in his decision on motions (Paper Number 60) for the purpose of distinguishing the subject matter of the count from the naturally occurring human protein. In response to the APJ's proposal to substitute the proposed count for the original count, the parties ultimately filed a joint motion to substitute what was defined as "Count 4" for proposed Count 2 (see Paper Number 98). The APJ granted the parties' joint motion and redeclared the interference to reflect the new count, designated as Count 3. (see Paper Numbers 99 and 100).

The native form of the protein of the count is a naturally occurring substance found in human cell media in a complex with

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trial upon the party on whom it was originally cast." See 37 C.F.R. § 1.671(b).

various metalloproteinase enzymes and other human proteins. While some human proteins react with the enzymes as substrates, some proteins prevent the enzymes from entering into reaction and are known as inhibitors. The protein of the count is one which inhibits (prevents) a particular form of an enzyme (latent, 72 kilodalton type IV collagenase) from degrading the extracellular matrix. Thus, because we find no ambiguity in the count, giving the language "purified and isolated" its broadest, reasonable interpretation without resort to any party's disclosure, we find the language means that the protein has been "purified and isolated" from its natural source to such a degree that the protein may be distinguished from the native, naturally occurring protein.

The first characteristic of the first alternative of the count requires that the purified and isolated human protein is a tissue inhibitor of metalloproteinases. Metalloproteinases are naturally occurring enzymes which degrade the extracellular matrix. Thus, a purified and isolated human protein which is a "tissue inhibitor" of metalloproteinases is a protein which forms a complex with the metalloproteinase enzyme thereby inhibiting the enzyme's function of cell degradation. Secondly, the count requires that the purified and isolated protein has a molecular weight from about 20 to about 28 kilodaltons. Third, the purified and isolated protein forms a complex with the latent form of the 72-kDa type IV collagenase

enzyme. Fourth, the purified and isolated protein has a specific amino acid sequence in its N-terminus as recited in the count.

The second alternative of the count is directed to a purified and isolated human protein defined solely in terms of its amino acid sequence "comprising" 194 specific amino acids. Because the second alternative of the count uses the open-ended term "comprising" so long as the isolated and purified protein has at least the particular sequence of the particular amino acids in the order recited in the count, the presence of other amino acids in the protein is not precluded.

GOLDBERG'S CASE FOR PRIORITY

According to Goldberg's preliminary statement (Paper Number 20), Goldberg first conceived of the invention defined by the count on October 26, 1986. Goldberg also alleges he began to exercise reasonable diligence towards reducing to practice the invention conceived on November 17, 1986. Goldberg also alleges to have actually reduced to practice the subject matter defined by the count on September 28, 1988.

According to Goldberg's brief, Goldberg conceived of the subject matter of the count on October 20, 1986, the date on which he first observed a complex between a protein and the 72 kDa type IV collagenase while developing a purification procedure for 72 kDa type IV collagenase secreted by transformed bronchial epithelial cells

(TBE-1). See Goldberg's brief at page 6; **JR** 1001-1003; and, **GX** 2. Goldberg has testified that the procedure for obtaining 72 kDa type IV collagenase and the structure of the cDNA clone encoding the 72 kDa enzyme which complexed with the protein was submitted for publication in September 1987 and published in May 1988. See **JR** 1002, paragraph (3) and **GX** 1. Goldberg alleges that he actually reduced to practice an embodiment within the count by September 28, 1988, when Barry L. Marmer, Goldberg's research assistant, purified and isolated a complex of the protein with the 72 kDa type collagenase and which protein was subsequently sequenced to yield the identical 22 amino acids of the **N**-terminal region of the first alternative of the count. See Goldberg's brief at page 7 and 8; **JR** 1003-1005; **GX** 4; **GX** 5; and **GX** 6; **JR** 1015-1017; and **GX** 13.

According to Goldberg's testimony, serum-free media conditioned by TBE-1 cells was chromatographed on various columns. While screening various columns, co-purification of the enzyme (72 kDa type IV collagenase) with a 24 kDa protein was revealed. Subsequently, the complex was "visualized" by SDS gel electrophoresing the protein/enzyme complex. Further analysis in 1988 of the complex yielded an **N**-terminal amino acid sequence of 22 amino acids (**GX** 5). In November 1988, Goldberg was able to separate the protein from the enzyme using gel filtration chromatography (**GX** 7)

and also separated the complex of TIMP-1 with the 92 kDa enzyme from the mixture.

Barry L. Marmer has testified that he carried out the experimental work described by Goldberg, above, and recorded the results in his various notebooks (**JR** 1016). Specifically, Marmer has testified that he personally carried out and recorded the experimental work set forth in his laboratory notebook, **GX** 2-8. On pages 147 and 148 of his notebook (**GX** 4 and **GX** 5, respectively), Marmer has testified that the heading "Mystery Protein at 21-23K from Run # 10 68K TBE [TIMP-2]" was a reference to the protein which formed a complex with the 72 kDa type IV collagenase which protein he isolated from the complex on September 27, 1988, and for which the N-terminal amino acid sequence of 22 amino acids was determined. On page 148 of Marmer's notebook Marmer explains that he cut out 2 proteins from the gel on page 147 and sent the 21-23K cut for sequencing on September 28, 1988. Attached to his notebook on page 148 are two lists which allegedly set forth the amino acid sequences for various proteins, including the 21-23K cut. In the column designated by what appears to be the notation "Run#2" the amino acid sequence:

SPVHPQQAFCNADVVIRAKAVS

is set forth for the amino acids designated as numbers 4 through 25. According to Marmer's testimony, the protein having the above-noted

sequence was designated as "TIMP-2" by Goldberg, as evidenced by Marmer's entry in the top his notebook on page 147 and made by him on September 28, 1988.

According to Goldberg's brief, when he obtained the 22 amino acid sequence for the "mystery protein" he actually reduced to practice an embodiment of the subject matter of the first alternative of the count because the protein had been purified and isolated from the TBE-1 cells in the form of the protein/enzyme complex and the protein had been further isolated from the complex and sequenced and determined to have the sequence in the **N**-terminal region required by the count. Thus, it is argued that Marmer had obtained a "purified and isolated human protein" which had a molecular weight of from "about 20 to about 28 kilodaltons (21-23K)" which formed a complex with the 72 kDa type IV collagenase and had the **N**-terminal amino acid sequence required by the count. According to Goldberg's brief, the recognition and appreciation that he had reduced to practice an embodiment within the count derived from the analogous complex formation between the closely related 92 kDa type collagenase and TIMP-1 known to exist at the time Marmer obtained the sequence for the "mystery protein."

STETLER-STEVENSON ET AL. CASE FOR PRIORITY

According to their preliminary statement (Paper Number 92), Stetler-Stevenson et al. allege to have conceived of the subject

matter defined by the count on July 12, 1988. Stetler-Stevenson et al. also allege to have started the exercise of reasonable diligence on July 12, 1988. Stetler-Stevenson et al. still further allege to have actually reduced to practice the invention defined by the count on July 28, 1988.

In their brief, Stetler-Stevenson et al. allege to have conceived the subject matter of the count on July 27, 1988, when after purifying and further analyzing three fractions obtained from the conditioned media of human melanoma cell line **A2058**, a ten amino acid sequence of the **N**-terminal sequence of the fraction denominated "Peak A" was obtained. The amino acid sequence obtained on July 27, 1988, was:

ESCSPVHPQQ

On December 5, 1988, Dr. Krutzsch allegedly recognized that the first amino acid was wrongly identified as glutamic acid, **E**, and should have been denominated as cysteine, **C** (**SSX** 6, **SSX** 7). In November 1988, it was discovered that the "Peak A" material was bound to the type IV collagenase (**SSX** 6). On November 18, 1988, more "Peak A" material obtained from serum-free conditioned media of **A2058** cells obtained from Dr. Stracke was obtained. In January 1989, fractions of the "Peak A" material were sent to Dr. Krutzsch for sequencing and the first 40 amino acids for the **N**-terminal residue of the "Peak A" material was obtained. The amino acid sequence obtained was:

CSCSPVHPQQAFCNADVVIRAKAVSEKEVPSGNPIYGNNI.

Homology searching revealed a partial homology and overlap in a 30 amino acid sequence with TIMP-1 (**SSX** 6; **SSX** 7). Drs. Stetler-Stevenson, Krutzsch and Liotta concluded the "Peak A" material was human tumor cell collagenase inhibitor and designated the material as "MCIP" (melanoma collagenase inhibitor protein) or TCCI (tumor cell collagenase inhibitor) (**SSX** 6).

During November and December 1988, the above results were repeated and confirmed. In January 1989, the purified and isolated protein inhibitor was subjected to endoproteinase Lys-C digest and the material obtained subjected to reverse phase HPLC to obtain peptide fragments. The fragments obtained were sequenced by Dr. Krutzsch (**SSX** 6; **SSX** 7). The results of this work was published in the Journal of Biological Chemistry in October 1989 (**SSX** 14). In March 1989, Dr. Stetler-Stevenson prepared and submitted an Invention Disclosure to the Office of Technology Transfer at NIH (**SSX** 15).

LANGLEY ET AL. CASE FOR PRIORITY

In their preliminary statement (Paper Number 105), Langley et al. allege to have conceived of the subject matter of the count on October 28, 1988. According to their preliminary statement, Langley et al. allege that they began the exercise of reasonable diligence on the date of conception, that is, October 28, 1988. Additionally, Langley et al. allege to have actually reduced to practice the

subject matter defined by the count in this interference on November 21, 1988.

By virtue of the granting of Langley et al.'s motion to deny Stetler-Stevenson et al. the benefit of their earlier filed application, Langley et al. are the senior party in this proceeding. See 37 C.F.R. § 1.657(a). As the senior party, Langley et al. need only prove priority of invention if one of the junior parties proves by a preponderance of the evidence a date of invention before Langley et al.'s effective filing date. Nevertheless, the statute requires in determining priority of invention that:

> there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. § 102(g) (1999). Accordingly, the period for which "reasonable diligence" must be shown by the junior parties depends on what date Langley et al. are afforded for conception. Therefore, if one of the junior parties proves a date of conception before Langley et al.'s effective filing date (Langley et al.'s constructive date of conception), we must also determine if Langley et al. have proved an earlier date of conception than any date proved by the junior parties.

According to their brief, Langley et al. assert that they had a complete conception of the invention defined by the count by

November 21, 1988, or not later than November 29, 1988. These dates represent, respectively, the dates on which Mr. Boone had determined the nucleotide sequence of certain clones isolated earlier in the month by Ms. Johnson. Using the sequence he actually determined for one of the clones, Mr. Boone "used that sequence to predict the sequence of human TIMP-2 protein." See page 10 of Langley et al.'s brief. Based on Mr. Boone's alleged recognition that the translation of human TIMP-2 protein would begin with the first methionine but that the signal sequence of the first 26 amino acids would be removed to produce a mature human TIMP-2 protein beginning at the first cysteine residue, Langley et al. urge that the amino acid sequences LX 25 and LX 26 are evidence of a conception of the subject matter of the second alternative of the count. See JR 2002, paragraph 7, 2003 and 2015-16.

Langley et al. rely, in part, on November 21, 1988, as their date of conception based on the alleged identity between the N-termini of bovine and human TIMP-1. According to Langley et al., a person skilled in the art of recombinant protein expression and possessed of the nucleotide and deduced amino acid sequence of TIMP-2, "could have expressed and purified the TIMP-2 protein using routine procedures without undue experimentation." JR 2004, paragraph 9. After November 21, 1988, Boone proceeded to express recombinant TIMP-2 in *E. coli* and, according to Langley et al., Boone did in fact

express in *E. coli* a TIMP-2 gene. See Langley et al.'s brief at pages 12 and 13. The gene expressed by *E. coli* is alleged to have been found to inhibit collagenase activity. **JR** 2061-62; **LX** 34.

In their brief, Langley et al. allege that in January 1989, Dr. Langley received a sample of TIMP-2 expressed from *E. coli* by Boone and Crandall. Dr. Langley testified that he electrophoresed the sample on SDS gel and that he concluded from the analysis that the sample given to him by Crandall was "highly purified." Dr. Langley further purified the sample on January 26, 1988, and his analysis of that sample indicated it, too, was pure. In February 1989, Ms. Fausset "confirmed" that the N-terminal amino acid sequence was the sequence predicted by Boone in November 1988. **JR** 2067, paragraph 5, **LX** 28, **LX** 37. By January 1989, tests demonstrated that a sample of recombinant TIMP-2 expressed from *E. coli* was an inhibitor of collagenase. By February 1989, Dr. Yean allegedly confirmed the results obtained earlier by Dr. Langley. See Langley et al.'s brief at page 22.

OPINION ON PRIORITY

GOLDBERG'S CASE FOR PRIORITY

It is by now well-settled that in order to prove an actual reduction to practice of an embodiment within the count, the party bearing the burden of proof must establish by a preponderance of the

evidence an actual reduction to practice of at least one embodiment including every element required by the count. Additionally, proof of an actual reduction to practice of every element required by the count must be corroborated.

Accordingly, in order to meet their burden of proof, Goldberg must establish that every limitation of the count in the interference existed in the embodiment relied on as an actual reduction to practice and the embodiment must be demonstrated to have performed as intended. Newkirk v. Lulejian, 825 F.2d 1581, 1582, 3 USPQ2d 1793, 1794 (Fed. Cir. 1987); Correge v. Murphy, 705 F.2d 1326, 1329, 217 USPQ 753, 755 (Fed. Cir. 1983); Parker v. Frilette, 462 F.2d 544, 548, 174 USPQ 321, 325 (CCPA 1972); Szekely v. Metcalf, 455 F.2d 1393, 1396, 173 USPQ 116, 119 (CCPA 1972); Schur v. Muller, 372 F.2d 546, 551, 152 USPQ 605, 609 (CCPA 1967).

It is by now well-settled that a chemical compound is actually reduced to practice when a compound meeting every limitation of the count is actually prepared and its utility demonstrated. Equally well-settled is the prerequisite that the actual reduction to practice must include a contemporaneous recognition and appreciation of the invention represented by the count by the inventor at the time the reduction to practice was made. Cooper v. Goldfarb, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998); Estee Lauder Inc. v. L'Oreal S.A., 129 F.3d 588, 593, 44 USPQ2d 1610, 1614 (Fed. Cir.

1997); Breen v. Henshaw, 472 F.2d 1398, 1401, 176 USPQ 519, 521 (CCPA 1973). Absent adequate identification and appreciation by the inventor that a compound within the count has actually been prepared, there can be no actual reduction to practice. There can be no actual reduction to practice without proving a physical embodiment which includes all the limitations of the count has been prepared. U.M.C. Electronics Co. v. United States, 816 F.2d 647, 652, 2 USPQ2d 1465, 1468 (Fed. Cir. 1987).

Goldberg's case is founded on the testimony of Goldberg, the named inventor of Goldberg's involved case, and the testimony and accompanying exhibits of Marmer, a non-inventor and Goldberg's research assistant. As the testimony of an inventor alone is inadequate to prove prior invention, Goldberg's case necessarily depends on the testimony and underlying exhibits of Marmer, both for what they actually show and for their corroborative value of Goldberg's testimony. Further, although Goldberg has alleged a theory of conception plus diligence up to his constructive reduction to practice in his preliminary statement as a basis for awarding him priority of invention, there is no argument made in Goldberg's brief for awarding him priority on a conception plus diligence theory. Accordingly, we limit our review of Goldberg's priority case to his alleged actual reduction to practice of an embodiment within the count prior to the senior party's effective filing date.

Goldberg relies on the submission and publication of his article in the Journal of Biological Chemistry in September 1987 and May 1988, respectively, as evidence of his recognition of the procedure for obtaining the enzyme and the cDNA clone encoding said enzyme which is a latent form of 72 kDa type IV collagenase. Goldberg alleges to have discovered a complex formed between the 72 kDa type IV collagenase secreted by transformed bronchial epithelial cells and "a protein." Goldberg relies on Marmer's notebook, pages 250 through 258 (**GX** 2) as evidence of the recognition of the formation of the complex and its purification. While this research was instrumental in the rest of Goldberg's research which led to his alleged reduction to practice, none of the aforementioned testimony or exhibits represents an actual reduction to practice of an embodiment including every limitation of the first alternative of the count.

Goldberg alleges that in September 1988, Marmer purified and isolated a complex of the protein which complexed with the 72 kDa type IV collagenase and that Marmer ultimately sequenced the purified and isolated protein. According to Goldberg, the sequence obtained had the identical 22 amino acids of the **N**-terminal region as is set forth in the first alternative of the count. Marmer's notebooks (**GX** 2 and **GX** 3) do show that Marmer was actively working on purifying the enzyme secreted by the transformed bronchial epithelial cells. That work was performed in 1986 but does not represent an actual reduction

to practice of an embodiment within the count. According to Marmer's testimony:

> The substance described in Goldberg Exhibits 4 and 5 as "Mystery Protein at 21-23 K from Run # 10 . 68 K TBE" was the protein complexed with the 72 kDa type IV collagenase which I isolated and purified from TBE-1 cells on September 27, 1988 ...

See JR 1016 at paragraph (5). Nevertheless, nothing in GX 4 describes the source of the "mystery protein" as the protein which formed a complex with the 72 kDa type IV collagenase. Rather, page 147 of Marmer's notebook (GX 4) includes the heading "Mystery Protein at 21-23 K from Run # 10 68 K TBE [TIMP #2]" and thereafter is set forth a narrative which recites that:

> On past runs a small MW band runs on 10% Gels either at the front or just above the front. Decided to submit samples for sequence.

Therefore, we cannot determine what basis exists in the underlying evidence, GX 4, for Marmer's testimony that the thing submitted for sequencing was, indeed, the protein of the count. At the bottom of GX 4, the following is set forth:

> O/N transfer to PVDF and cut out bands

We understand this passage to mean that overnight ("O/N") the separated bands were transferred to a polyvinylidine fluoride film for sequencing.

Marmer has testified that his notebook page 148 (GX 5) includes the amino acid sequence obtained for the isolated and

purified protein obtained on page 147 (**GX** 4) of his notebook. At the top of page 148, Marmer wrote the following:

> Cut out 4 x 21-23K ~4 mg ea
> 4 x 68K only ~ 20 mg ea
> no active
> Sent over 21-23 K for sequence on 9/28

Attached to the bottom of page 148 are what appear to be two overlays of paper with several columns of information set forth thereon. Above the left-most overlay are the words "first 2 ~ 8mg" and above the right-most overlay are the words "Second repeat of 8 mg". The overlays are themselves undated but Marmer has testified that the sequence "was determined on the next day (September 28, 1988)."

In the right-most overlay on **GX** 5, under the column headed "Run #2", an amino acid sequence is set forth for amino acids 2 and 4 through 26 of a 26 amino acid sequence. The sequence set forth reads as follows:

S SPVHPQQAF(C)NADVVIRAKAVS(T)

While the significance of the parenthesis has not been explained, it appears from the notebook page that the parenthesis indicated that the person sequencing the amino acid sequence had some uncertainties about the amino acid specifically designated for a particular position. We base that conclusion on the handwritten but also unexplained notations on the left most overlay such as "definitely not **Val**"; "definitely **Val**"; "definitely **Gln**"; "definitely **Ala**"; and,

"definitely **Val** - no leu present." Marmer testified that the amino acid sequence on **GX** 5 corresponded to the isolated and purified protein set forth on **GX** 4 and designated by Goldberg as "TIMP # 2" as entered by Marmer on **GX** 4. See **JR** 1016-17.

We find that Goldberg's evidence of an actual reduction to practice lacks proof of any connection between the "mystery protein" isolated and sequenced and the complex formed between the 72 kDa latent form of collagenase type IV enzyme. There is no reference, either express or inferential, in either **GX** 4 or **GX** 5 which are dated in September 1988 to Marmer's earlier work in **GX** 2 or **GX** 3 and performed in 1986. Indeed, neither **GX** 2 nor **GX** 3 refer to any complex between the enzyme (protease) and <u>any</u> protein let alone the particular protein of the first alternative of the count. Rather, **GX** 2 and **GX** 3 are directed to the purification of an enzyme secreted by transformed bronchial epithelial cells. Further, the thrust of **GX** 1 may be found on page 6584 thereof wherein the authors conclude:

> Based on these observations, we conclude in all likelihood, the 72-kDa gelatinase represents a single enzyme, secreted by TBE-1 cells, capable of degrading type IV collagen.

There is no mention in **GX** 1 of the ability of type IV collagenase to form a complex with a protein as required by the first alternative of the count. Rather **GX** 1 is entirely directed to obtaining from TBE-1 cells the enzyme which came to be named type IV collagenase.

Because Goldberg has not proffered any evidence showing the complete amino acid sequence for the protein defined by the second alternative of the count, Goldberg's proofs necessarily must go to the first alternative of the count. The first alternative of the count requires a "purified and isolated human protein", which protein is a "tissue inhibitor of metalloproteinases" and forms a complex with the "latent form of the 72-kilodalton type IV collagenase", which protein has a molecular weight of from about 20 to about 28 kilodaltons and which protein has a particular N-terminal amino acid sequence. Goldberg's testimony and documentary evidence establish that Marmer had isolated and purified a "mystery protein" from human TBE-1 cells and that said isolated and purified "mystery protein" had an amino acid sequence corresponding to the sequence required by the first alternative of the count. There is no evidence, however, establishing that the "mystery protein" was recognized at the time Marmer's notebook entries were made in **GX** 4 and **GX** 5 as a "tissue inhibitor of metallo proteinases" or that the "mystery protein" formed a complex with the "latent form of the 72-kilodalton type IV collagenase."

Although Goldberg alleges in his brief that the "mystery protein" was, in its native form, "complexed with the 72 kDa type IV collagenase", there is no evidence in either **GX** 4 or **GX** 5 which supports that allegation. Reliance on **GX** 1 as evidence that the

purification procedure for obtaining type IV collagenase and the structure of the enzyme were known in 1987 does not aid Goldberg in proving that the protein of the first alternative of the count was known before the senior party's effective filing date. As we have found above, there is no mention in **GX** 1 of the protein of the first alternative of the count. Further, although Goldberg testified that **GX** 2 includes evidence that a complex was observed between the enzyme and the protein of the count (see **JR** 1002-1003), nothing in Marmer's testimony or the exhibit itself evidences the formation of any complex of the enzyme with any protein. Nor has Goldberg directed us to the specific page and disclosure in **GX** 2 on which he relies for his allegation. Still further, as we have stated above, the first alternative of the count requires that the protein of interest forms a complex with the latent form of the 72 kDa type IV collagenase. The reference at the top of **GX** 4 and **GX** 5 to a "68K TBE" appears to denote the active form of the enzyme rather than the latent form. See **GX** 1 at page 6586, column 1, lines 56 through 60, wherein it is recited that:

> Although the amino-terminal sequence of activated type IV collagenase has not yet been determined, it is likely that conversion to the 66-kDa active enzyme form is the result of processing of the amino-terminal portion of the protein.

See also page 14, lines 25 through 31 of **LX** 11. Therefore, whatever the "mystery protein" formed a complex with it was not with the

latent form of the 72-kDa type IV collagenase required by the first alternative of the count.

Even assuming, *arguendo*, that the evidence on which Goldberg relies does show the protein forms a complex with the latent form of the enzyme, there is no evidence contemporaneous in time in any of the proofs on which Goldberg relies which establishes Goldberg recognized any practical utility for the protein. While Goldberg alleges practical utility was demonstrated by "similarity of a property of the novel protein to an established property of a known class of proteins having known utility." (see page 10 of Goldberg's brief), nothing in the evidence supports that allegation.

According to Goldberg's brief, the utility for the protein was "demonstrated" by its ability to form a complex with the 72 kDa type IV collagenase. Goldberg cites Landon v. Ginzton, 214 F.2d 160, 102 USPQ 230 (CCPA 1954) in support of his argument. Nevertheless, Landon does not support Goldberg's argued position. Rather, the court in Landon specifically found that:

> It is elemental that an invention must be shown to be of practical utility for its intended purpose, and unless the device and its use be very simple or obvious, it is necessary that the practicability be demonstrated by actually building and testing the device embodying the invention under the conditions it would be expected to encounter in such use.

214 F.2d at, 102 USPQ at 233. Here, the invention, a human protein, is not so "simple" in nature as to suggest or render obvious any practical utility.

Nor does Bindra v. Kelly, 206 USPQ 570 (BPAI 1979), cited by Goldberg, support Goldberg's argued position. The Board held in Bindra that practical utility for a novel compound must be established before the novel compound may be said to have been reduced to practice. 206 USPQ at 575. The Board also held that only where sufficient properties of the novel compound were determined and shown to be similar to established properties of a known class of compounds having a known utility could practical utility be said to be established for the novel compound. Based on the facts in Bindra, the Board went on to conclude that even a high degree of probability that a novel compound would function in the same manner as a group of known compounds did not establish practical utility. Rather, the Board concluded that probable utility does not establish practical utility. Id.

The only evidence alluded to in Goldberg's brief which shows any relationship between the novel protein of the count, also denominated as TIMP-2, and TIMP is found in GX 11, Goldberg's involved application. Aside from the fact that the date of Goldberg's application is subsequent to the senior party's effective filing date and, thus, may not be relied on to prove prior invention, GX 11 does

not show a similarity of properties between TIMP-2 and TIMP such that practical utility for TIMP-2 can be reliably predicted from the properties of, and practical for, TIMP. Specifically, at page 3 of GX 11, it is disclosed that TIMP "complexes exclusively with the 92-kDa type IV collagenase." Moreover, although TIMP-2 is characterized as demonstrating partial homology to TIMP, as shown by a comparison of the two protein's partial amino acid sequences, it is specifically disclosed that TIMP-2 does not "cross-react with TIMP specific antibody." Accordingly, we find that Goldberg's theory advanced under Bindra fails to establish a practical utility for the "mystery protein" described in GX 4 and GX 5 based on the evidence here before us.

Although Goldberg's brief includes a section entitled "Conception" and although Goldberg has alleged to have conceived of the subject matter of the count before Langley et al., because Goldberg has not advanced any argument or evidence concerning the exercise of reasonable diligence, we need not address what date, if any, we accord Goldberg for a conception of the subject matter of the count. Without proof of reasonable diligence, proof of conception, standing alone, of a prior conception of the subject matter of the count does not entitle Goldberg to an award of priority. Accordingly, for all the above reasons, we find that Goldberg has failed to demonstrate by a preponderance of the evidence that he actually

reduced to practice an embodiment within the first alternative of the count prior to Langley et al.'s effective filing date.

STETLER-STEVENSON ET AL.'S CASE FOR PRIORITY

In view of the granting of Langley et al.'s motion to deny Stetler-Stevenson et al. the benefit of their earlier filed application, Stetler-Stevenson et al. are a junior party in this interference.[9] Accordingly, Stetler-Stevenson et al. bear the burden of proving priority of invention by a preponderance of the evidence. In their preliminary statement, Stetler-Stevenson et al. alleged prior invention based on an earlier conception than the senior party coupled with "reasonable diligence" up to a reduction to practice by them. Stetler-Stevenson et al. also alleged prior invention based on an actual reduction to practice before the senior party's effective filing date.

Before we render our decision on the merits of Stetler-Stevenson et al.'s priority case, we are compelled to comment on the quality of some of the evidence on which they rely. Stetler-Stevenson et al. substantially rely on parts of Dr. Stetler-Stevenson's notebook which is **SSX** 6. The pages of the exhibit do not bear Bates numbers but, instead, the exhibit is a collection of what appear to be copies of pages from a notebook, some of which bear printed numbers, some of which appear to

[9] See 37 C.F.R. § 1.601(m) (2002).

be pages of printouts from analytical instruments which were either taped into the notebook or simply inserted between certain pages of the notebook, and, apparently, also pages from other, unidentified notebooks. Many of the pages are undated. Many of the pages in **SSX** 6 bear neither the signature nor initials of Dr. Stetler-Stevenson. No page in **SSX** 6 appears to have been witnessed.

The exhibit **SSX** 7 appears to be a compilation of log book entries for an amino acid sequencer with accompanying spectra and readouts. Dr. Krutzsch has testified that the log entries were recorded by him as part of his records. **JR** at page 3013. Again, the pages of the exhibit are not Bates numbered and the correlation, if any, between the attached spectra and readouts and the log entry is not apparent. Many of the references to **SSX** 7 are made simply by reference to an alleged date on which a particular analysis was allegedly performed. See, for example, **JR** at page 3015, paragraph 10. Many of the pages in **SSX** 7 are not dated. None of the pages in **SSX** 7 is witnessed.

It is a party's duty under the rules to include in their arguments the underlying reasons for their arguments with specific citations to the record, statutes and case law which supports the arguments made. It is not the responsibility of this Board to search through the record to find the evidence which may support a party's arguments from their brief. We are reminded of a statement made by

the court in United States v. Dunkel, 927 F.2d 955, 956 (7th Cir. 1991):

> Judges are not like pigs, hunting for truffles buried in briefs.

Alluding to an alleged fact in a multi-page exhibit based on the date of entry for a particular page places this Board in the position of having to search the exhibit to find the alleged fact which may support the position taken by the party in their brief. This places both this Board and the senior party in the position of not actually knowing which fact or authority supports the position taken in the brief. More importantly, it places this Board in the position of having to advocate a position on behalf of the party making the argument based on the Board's determination of what in the record supports the position taken. We cannot condone such role-shifting. Stetler-Stevenson et al. have also included in their brief a section required by the rules and headed "**STATEMENT OF FACTS.**" Therein, in numbered paragraphs, Stetler-Stevenson et al set forth "facts" in support of the positions taken by them in their brief.

According to their brief, Stetler-Stevenson et al. conceived of the subject matter of the count not later than July 27, 1988, "when the first ten amino acid sequence for the material Peak A with a retention time of ~27 min. was obtained." Stetler-Stevenson et al. brief at pages 10 and 11. The basis for this argument appears to

be found in **SSX** 6. However, we have not been directed to a page in **SSX** 6 which establishes that Stetler-Stevenson et al. conceived of an embodiment within the count wherein each limitation defining the subject matter of the count may be found. We are told that Dr. Stetler-Stevenson labeled the peak representing the component with a retention time of about 27 minutes as a "major contaminant" on July 15, 1988. **SSX** 6 at page 37. Specifically, page 37 of **SSX** 6, which is dated "JUL 15 1988", has written therein the following statement:

> Based on the expected hydrophilicity of type IV collagenase it is expected that the peak with the retention time >30 min is purified type IV collagenase and that this prep is about 90% purified with a single major contaminant corresponding to ~10% of the material present.

Page 39 of **SSX** 6, dated July 17, 1988, discusses the preparation of a gelatin sepharose column and on the same page under the handwritten date of "7-18-88" discusses the loading and collection of samples using the sepharose column prepared on July 17, 1988. Samples of the combined fractions were "aliquoted and stored frozen at -7°C." The next page in **SSX** 6, which is both unnumbered and undated, is a printed spectrum of an unidentified sample showing two major peaks labeled with the handwritten notations "**A**" and "**B**".

On the next page of **SSX** 6, which bears the page number 41 and is dated "Jul 19 1988", is a heading "HPLC Purification of Type IV Collagenase for Direct Amino Acid Sequencing." Between the words

"of" and "Type" there is a caret denoting an undated insertion of the word "latent." Thereafter, the following is set forth:

> 100 µl of gelatin sepharose purified [material] type IV collagenase prep 7-18-88 was subjected to reverse phase (C18) HPLC. The material in the peak with a retention time > 30 min was collected and subjected to direct amino acid sequencing
>
> Eight residues sequence
> **APSPIIKF**

Alongside the above noted sequence is a date stamp "JUL 19 1988" and what appears to be an illegible word or initials.

The next page of **SSX** 6 is a notebook page numbered "43." Beneath the page number is a date stamp "JUL 25 1988." The page is headed "HPLC Purification of pAPMA Activated Type IV Collagenase for Amino Acid Sequencing." Thereafter, the procedure carried out is described as:

> 300 µl Purified Type IV collagenase 7-18-88 in 1x collagenase buffer was made 1.0 MM in pAPMA by addition of 33 µl of 10 MM pAPMA stock (freshly prepared) and incubated at 37°C for 18 hours.
>
> This material was subjected to reverse phase HPLC on 7-26-88 and the peak at ~30 min was collected and subjected to direct amino acid sequencing.
>
> 10 residues sequenced
> **YNFFPRKPKW**
> This data suggest that a new amino terminus is generated during pAPMA treatment of type IV collagenase and confirms the observation that on Western blotting during the time course of pAPMA activation the reactivity with antibody A1-17 (H1 antibody) is gradually lost

Just below the above noted entry on the right hand side of the page is a date stamp "JUL 25 1988."

The next page in **SSX** 6 is an unnumbered, illegible printout of some analytical instrument for an unidentified sample. The tops of two otherwise unidentified partial peaks denominated "**A**" and "**B**" are found on the edge of the exhibit. The next page of **SSX** 6 is a notebook page numbered "44" with part of a printout from some analytical instrument attached to the page. Overlying the printout and perhaps attached to the notebook page is an unsigned, undated note bearing the following notation:

> **UNKNW**
> Glu-Ser-Cys-Ser-Pro-Met-His-Pro-
> **ESCSPMHPQQ**

The next page in **SSX** 6 is an unnumbered printout overlying an unidentified notebook page with a date stamp "JUL 27 198" visible at the bottom right corner of the exhibit. The printout bears the heading "Sample Name: ACT TYPE-IV COLL/1AUFE Date: Thu Jul 28 14:17:38 1988." On the printout below there are two peaks denominated as peak "**A**" and peak "**B**."

The last page from **SSX** 6 which is said to support Stetler-Stevenson et al.'s alleged conception of the subject matter of the count by not later than July 27, 1988, is the page numbered "45" bearing a date stamp of "JUL 27 1988." The page is headed "Repeat

HPLC purification and Sequencing." After setting forth the procedure used to treat the type IV collagenase with pAPMA, the sample was subjected to "Reverse HPLC analysis and both peaks were [subjected] collected for direct sequencing." Around mid-page there is the following notation:

> Peak 8 on HPLC
> 15 residues sequenced
> **YNFFPRKPKWDKNQI**

Below the sequence is the following observation:

> when compared with the amino terminal sequence of type IV collagenase prior to pAPMA activation obtained on 7-19-88 this data demonstrates that pAPMA treatment results in loss of an amino terminal fragment.

Below the first sequence is another notation as follows:

> Peak 6 on HPLC Profile
> 10 residues sequenced
> **ESCSPVHPQQ**

Below the sequence there is an arrow directed at the first amino acid of the sequence followed by the notation "originally called **E** see 12/8/88" with someone's illegible initials after the date, possibly Dr. Stetler-Stevenson's initials.

The above noted evidence constitutes the entirety of Stetler-Stevenson et al.'s documentary evidence in support of their argument that they conceived the subject matter of the count by not later than July 27, 1988. We are also directed to the testimony of Dr.'s Stetler-Stevenson, Liotta and Krutzsch, the named inventors of

Stetler-Stevenson et al.'s involved application, as evidence of conception by not later than July 27, 1988. For reasons set forth below, we find that Stetler-Stevenson et al. have not met their burden of persuasion and established by a preponderance of the evidence that they conceived of the subject matter of the count by not later than July 27, 1988.

In order to prove their case for priority Stetler-Stevenson et al. must show that the subject matter of the count was conceived by them at a time before the senior party's effective filing date or the senior party's earliest proven date of conception. Stetler-Stevenson et al.'s documentary evidence and testimony fail to establish that they conceived of the subject matter of the count, a purified and isolated human protein which is a tissue inhibitor of metalloproteinases having a molecular weight of from about 20 to 28 kDa, which forms a complex with the latent form of the 72 kDa type IV collagenase, and which has a twenty-two amino acid N-terminal amino acid sequence of **SPVHPQQAFCNADVVIRAKAVS**.

The evidence for the work performed during the time period of from July 15, 1988, through July 27, 1988, does not describe an isolated and purified human protein as required by the first alternative of the count. We agree with Langley et al.'s argument that the work set forth in Dr. Stetler-Stevenson et al.'s notebook was primarily directed to purifying type IV collagenase. See numbered

notebook pages 33 and 35 of **SSX** 6. The notebook page numbered 37 in **SSX** 6 at best establishes that the reverse phase HPLC separated sample was comprised of two components, one believed to be the purified type IV collagenase secreted by the **A2058** melanoma cell line and represented by the retention time greater than 30 minutes, and the other a contaminant of unknown identity and represented by a retention time of about 27 minutes. Accepting for the sake of argument that the interlineation "latent" on numbered notebook page 41 was made on July 19, 1988, the procedure followed on page 41 was for the collection and sequencing of the material with the retention time of greater than 30 minutes, that is, the purified type IV collagenase. It is that material whose sequence is set forth for 8 residues on the same page. Suffice it to say that the sequence set forth on page 41 is not for the protein of the count and is not the sequence required by the count.

Again, at page 43 of **SSX** 6, the material sequenced was the material under the peak with the retention time of greater than 30 minutes, that is, the enzyme, type IV collagenase. What is shown by page 43 is that activation of the enzyme with organic mercurials changes the amino terminal sequence of the enzyme. This evidence does not support a conception of the subject matter of the count which is directed to a protein which binds to a latent form of the enzyme not the enzyme itself. The page numbered 44 in **SSX** 6 is undated and the

apparent amino acid sequence set forth on what appears to be an attachment to the notebook page is not identified. Whatever sample was sequenced to obtain the sequence set forth on page 44, the sequence is not the sequence required by the count.

The page numbered 45 in **SSX** 6 shows that more type IV collagenase was activated with organic mercurials and subjected to reverse phase HPLC. Apparently, reverse phase HPLC resulted in obtention of material represented by two peaks, both of which materials were collected and sequenced. From the commentary on page 45 concerning the comparison of the activated collagenase sequence compared to the unactivated sequence, the "Peak 8" sequence is not for the subject matter of the count but for the enzyme itself. The material identified as "Peak 6 on HPLC Profile" on page 45 is not otherwise identified. Suffice it to say that the 10 amino acid sequence set forth is not the 22 amino acid sequence required by the count.

Stetler-Stevenson et al. also rely on the testimony of the inventors as evidence of conception. Specifically, Stetler-Stevenson et al. rely on the testimony of Dr. Krutzsch (**JR** 3023-3025), Dr. Liotta (**JR** 3010) and Dr. Stetler-Stevenson (**JR** 3042-3045) as evidence that the inventors "were sure that they had obtained the purified type IV collagenase inhibitor." See page 11 of Stetler-Stevenson et al.'s brief. Nevertheless, for reasons set forth fully below, the

inventors' testimony does not prove by a preponderance of the evidence, either alone or considered with Stetler-Stevenson et al.'s other evidence, that they conceived of the subject matter of the count not later than July 27, 1988, as alleged. Additionally, as the relied upon testimony is the testimony of the inventors themselves, it requires corroboration.

Dr. Krutzsch's testimony suggests that Dr. Stetler-Stevenson eluted bound material from "the affinity column and the gelatin sepharose column" (**JR** page 3023 at paragraph 3) and the eluted material contained two proteins as evidenced by **SSX** 6, page 26. But page 26 is only an undated page which appears to have a poor very dark copy of the results of an otherwise unidentified SDS gel chromatography attached to the page. We find page 26 of **SSX** 6 to be of little, probative value. According to Dr. Krutzsch's testimony, on July 12, 1988, Dr. Stetler-Stevenson used reverse phase HPLC to separate the two proteins evidenced by the gel electrophoresis on page 26 and obtained a chromatogram having two peaks. Dr. Krutzsch testified that the peaks were identified as type IV collagenase (Peak "**B**") and "the inhibitor" (Peak "**A**"). But page 29 of **SSX** 6, dated July 12, 1988, only tentatively identifies one of the two materials, the Peak "**B**" material, by describing it as "thought to be type IV collagenase." This is <u>not</u> evidence of conception of the subject matter of the count. Contrary to Dr. Krutzsch's testimony, nothing in

SSX 6 at pages 44 and 45 identifies the sequenced material as the Peak "**A**" material. More importantly, the 10 (ten) amino acid sequence for the material identified as "Peak 6 on HPLC Profile" on page 45 of **SSX** 6 is not the 22 (twenty-two) amino acid sequence required by the count.

Except for Dr. Krutzsch's testimony that he and Dr.'s Stetler-Stevenson and Liotta discussed the results obtained by Dr. Stetler-Stevenson and decided to eliminate any doubt that the Peak "**A**" material was a contaminant from the media used to culture the **A2058** melanoma cells, there is no documentary evidence (such as a report, an e-mail or a memorandum) of any discussion between the inventors which supports Dr. Krutzsch's testimony. Nothing in **SSX** 6, pages 98 through 104, and spanning the time from December 2, 1988, through December 5, 1988, supports Dr. Krutzsch's conclusion (**JR** 3024, paragraph 7) that the Peak "**A**" material was identified as "the inhibitor of Type IV collagenase" let alone recognized as an embodiment of the subject matter of the count.

Dr. Krutzsch's testimony that the material collected under Peak "**A**" was sequenced and that a degree of sequence homology to bovine and human tissue inhibitor metalloproteinase was found does not establish a conception of the subject matter of the count. Considering page 109 from **SSX** 6 in a light most favorable to Stetler-

Stevenson et al., ignoring the amino acid leader sequence "CSC", and then adding the amino acids "AKAVS" denominated as amino acids 21 through 25 to the sequence for amino acids 4 through 20, page 109 does not show conception of an isolated and purified human protein having a molecular weight of from 20 to about 28 kDa which forms a complex with the latent form of the 72 kDa type IV collagenase, as required by the first alternative of the count.

Dr. Liotta's testimony is, generally, to the same effect as Dr. Krutzsch's testimony. Specifically, Dr. Liotta testified that, because Dr. Stetler-Stevenson obtained enzyme from fetal calf conditioned media of human A2058 melanoma cell line, he wanted to eliminate the possibility that what he obtained might have been a contaminant from the fetal calf serum. While Dr. Liotta testified that after the material collected using fetal calf serum free media was sequenced and the sequence compared to known bovine and human metalloproteinases, the homology "confirmed" the inventors' belief "that Peak A was the purified and isolated inhibitor of type IV collagenase", the underlying factual basis for his conclusion is not found in the evidence of record.

Dr. Stetler-Stevenson, too, testified that he repeated his experiments from July 1988 but with fetal calf serum-free media to remove the possibility that what he had obtained before was not a contaminant from the fetal calf serum. JR 3042-3043, paragraph 7.

While Dr. Stetler-Stevenson has testified that he believed the material present in Peak **A** was a human inhibitor of Type IV collagenase, the documentary evidence on which Stetler-Stevenson et al. rely establishes that on July 15, 1988, he believed it to be only "a single major contaminant corresponding to ~10% of the material present." **SSX** 6 at page 37. Further, while Stetler-Stevenson et al. urge that they conceived of the subject matter of the count not later than July 27, 1988, Dr. Stetler-Stevenson has testified that the fetal calf serum-free media was first used by him in November 1988! We find that Stetler-Stevenson et al. could not have been certain that the results they obtained were not a contaminant from the fetal calf serum at a time, July 1988 (**JR** 3042-3043), before they used the fetal calf serum free media. See **JR** 3044, paragraph 9.

Stetler-Stevenson et al. have argued that, because conception has been defined as requiring proof of (1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it, their evidence of obtaining the first ten amino acids in the **N**-terminus of the protein from Peak "**A**" (the "idea" of the structure) and the isolation and purification of TIMP-2 (possession of an operative method of making the compound) meets the legal requirements for proving conception. We disagree.

As we understand Stetler-Stevenson et al.'s argument, they urge that at the time Dr. Stettler-Stevenson obtained a 10 amino acid

sequence for the N-terminus of the protein he obtained on July 27, 1988 (**SSX** 6, page 45; **SSX** 7, sequence log dated 7/27/88), the inventors were in possession of an idea of the structure of "TIMP-2" and also were in possession of a method for making "TIMP-2." Glaring by its absence in the record, however, is any evidence which explains how Stetler-Stevenson et al. were able to envision the subject matter of the count when the sequence for the material they prepared was only 10 amino acids not 22 amino acids as required by the count. Also absent from their proofs is any substantial objective evidence which proves that what they had obtained in July 1988 would have been understood by them in July 1988 to have the utility required by the count (tissue inhibitor of metalloproteinases). None of Stetler-Stevenson et al.'s proofs prove they had conceived of, or had obtained, a purified and isolated human protein with a molecular weight between 20 and 28 kDa. There is no evidence in the record on which Stetler-Stevenson et al. rely of "a definite and permanent idea of the complete and operative invention, as it is therefore to be applied in practice." Kridl v. McCormick, 105 F.3d 1446, 1449, 41 USPQ2d 1686, 1689 (Fed. Cir. 1997). The "invention" is, of course, the subject matter defined by the count. Because the 10 amino acid partial sequence of the 22 amino acid sequence required by the first alternative of the count cannot be a conception of the subject matter of the count, it necessarily follows that Stetler-Stevenson et al.

could not have conceived of a method for making the subject matter of the count based on their inadequate proofs of the structure of the protein of the count.

In reaching our conclusion that Stetler-Stevenson et al.'s proofs of conception are inadequate, we have not even addressed the requirement for corroboration. It is well-established that where the party with the burden of proof attempts to prove conception solely by evidence from the inventors, that party must proffer evidence corroborating the inventors' evidence. Mahurkar v. C.R. Bard, Inc., 79 F.3d 1572, 1577, 38 USPQ2d 1288, 1290 (Fed. Cir. 1996); Price v. Symsek, 988 F.2d 1187, 1194-95, 26 USPQ2d 1031, 1036-37 (Fed. Cir. 1993). As the evidence on which Stetler-Stevenson et al. rely is either the notebooks of Dr. Stetler-Stevenson, one of the inventors, the amino acid sequencer logs of Dr. Krutzcsh, one of the inventors, or the inventors' testimony, there must be corroboration by non-inventors, independent of the inventors. The record lacks any evidence of adequate corroboration.

Just as proofs of an actual reduction to practice must show that every element of the count was actually reduced to practice, a party's evidence of corroboration must corroborate each of the prerequisites for a conception or an actual reduction to practice. It is by now well-settled that an inventor must provide independent corroborating evidence in addition to his own statements and

documents. Lacotte v. Thomas, 758 F.2d 611, 613, 225 USPQ 633, 634 (Fed. Cir. 1985). The evidence establishing corroboration "may consist of testimony of a witness, other than an inventor, to the actual reduction to practice or it may consist of evidence of surrounding facts and circumstances independent of information received from the inventor." Reese v. Hurst, 661 F.2d 1222, 1225, 211 USPQ 936, 940 (CCPA 1981) (emphasis ours).

The evidence necessary for corroboration is determined by the so-called "rule of reason" which involves an examination, analysis and evaluation of the record as a whole to the end that a reasoned determination as to the credibility of the inventor's story may be reached. Berges v. Gottstein, 618 F.2d 771, 774 [n.5], 205 USPQ 691, 694 [n.5] (CCPA 1980); Mann v. Werner, 347 F.2d 636, 640, 146 USPQ 199, 202 (CCPA 1965). It has been recognized that whether an actual reduction to practice has been corroborated must be decided on the facts of each particular case. Berges v. Gottstein 618 F.2d at 776, 205 USPQ at 695. Nonetheless, adoption of the "rule of reason" has not dispensed with the requirement that corroborative evidence must not stem from the inventor himself but must be independent of information received from the inventor. Reese v. Hurst, *id.*, Mikus v. Wachtel, 542 F.2d 1157, 1159, 191 USPQ 571, 573 (CCPA 1976).

According to Stetler-Stevenson et al. their alleged conception and actual reduction to practice were corroborated by Anna

Levy, Dr. Sobel, Dr. Stracke and Dr. Aznavoorian. Anna Levy's testimony at JR 3066-3069 is relied on for corroboration. However, her testimony is largely her unsupported recollection of the collective efforts of Dr.'s Stetler-Stevenson, Liotta and Krutzsch some 12 (twelve) years after the events recalled and her unspecific recollection that she was "able to observe" Dr. Stetler-Stevenson's work "every day." Ms. Levy's recollection of data allegedly presented by her at meetings some 12 (twelve) years prior to her testimony, without any underlying documentary evidence supporting her recollections, are not given much weight. Although Ms. Levy recalls that the inventors "reported the co-purification of the inhibitor with Type IV collagenase and the sequencing of the inhibitor by Dr. Krutzsch in the period of July 1988 to February 1989", there is no objective evidence which supports her testimony. There is simply no evidence, contemporaneous in time with the alleged conception and actual reduction to practice, which corroborates any of the allegations made by Stetler-Stevenson et al. in their brief. But more significantly, Ms. Levy's testimony does not corroborate either the conception or reduction to practice of any specific embodiment within the count by any of the inventors.

Similarly, Dr. Sobel's testimony lacks evidence contemporaneous in time with the inventors alleged conception and actual reduction to practice which would corroborate the allegations

made by Stetler-Stevenson et al. At best, Dr. Sobol's testimony and accompanying notes from September 27, 1988, some two months after the conception alleged by Stetler-Stevenson et al. and almost three months before the alleged actual reduction to practice, establish that an enzyme secreted as latent procollagenase degrades type I gelatin but not type IV collagen which "implies diff enzyme mechanisms." The relevance of those notes to the subject matter of the count is not apparent to this Board. Moreover, Dr. Sobol's testimony cannot corroborate the actual reduction to practice because his notes about Dr. Stetler-Stevenson's research were made before the alleged actual reduction to practice occurred.

Dr. Stracke has testified that she prepared large quantities of serum-free conditioned media from the human melanoma cell line A2058 in November 1988. Although Dr. Stracke recalls that she gave quantities of the conditioned media to Dr. Stetler-Stevenson, she has testified that she "did not, however, routinely record this in my notebook." JR 3072. While Dr. Stracke has testified that the inventors used the media to obtain type IV collagenase and ultimately separate the enzyme from a "co-purifying protein", there is no evidence of record which supports her recollections. Although Dr. Stracke recalls meetings held on a weekly basis over a two year period in which the inventors discussed their "results", there is no evidence of record of such meetings or any other evidence which

supports her recollections. Most significantly, there is no evidence in Dr. Stracke's testimony which corroborates either a conception or actual reduction to practice of any embodiment of the invention defined by the count, including all its limitations.

Dr. Aznavoorian is alleged to have recognized that the inventors "had the inhibitor." See page 12 of Stetler-Stevenson et al.'s brief. We are directed to paragraph nine of Dr. Aznavoorian's declaration (JR 3094) in support of Stetler-Stevenson et al.'s allegation. In paragraph nine Dr. Aznavoorian testified that she was aware of the inventors' success in "isolating, purifying and partially sequencing TIMP-2 at least in July of 1988." According to her testimony, the inventors communicated to their colleagues, including Dr. Aznavoorian, that they "had isolated and purified TIMP-2." Nevertheless, there is no underlying evidence which establishes that the inventors communicated to their colleagues in the critical period of around July 1988 any information about their research let alone that the inventors had isolated, purified and partially sequenced TIMP-2. We have not overlooked Dr. Aznavoorian's testimony in paragraph eleven of her declaration wherein she testified that on December 8, 1988, she signed and dated a page from Dr. Liotta's notebook "confirming" the sequence for the N-terminus of TIMP-2. SSX 32.

The exhibit **SSX** 32 is an unnumbered page to which is attached or overlaid a printed paper headed "**PURIFIED TYPE IV COLLAGENASE AMINO TERMINAL SEQUENCE**" which has directly below the heading three amino acid sequences headed "**LATENT**"; "**ACTIVATED**" and "**CLEAVAGE SITE.**" Directly below the attached or overlaid printed paper are handwritten notes identified only as "**S:**", "**O:**", "**A:**" and "**P:**" The notes apparently attributed to "**S**" state:

> Identification of a novel natural metalloproteinase inhibitor.

The notes apparently attributed to "**O**" state:

> A 19 kDa protein which copurified with type IV collagenase on gelatin affinity chromatography of **A2058** melanoma cell conditioned media was isolated and sequenced directly.
>
> **Cys-Ser-Cys-Ser-Pro-Val-His-Pro-Gln--Gln-Ala-Phe-Cys-Asn-Ala-Asp-Val-Val-Ile-Arg-Ala-Lys-Ala-Val-Ser-Glu-Lys-Glu-Val-Asp-Ser-Gly-Asn-Pro**
>
> A 63% identity was found with human metalloproteinase inhibitor precursor.

Thereafter, notes attributed to "**A:**" recite that:

> New natural inhibitor of metalloproteinases.

And thereafter, notes attributed to "**P:**" recite:

> Clone to obtain entire sequence

At the bottom of the page are the signatures of Dr.'s Liotta, Krutzsch and Stetler-Stevenson and under a note which states "Read

and Understood", the signature of Sadie Aznavoorian. All the signatures are dated "12/8/88."

Thus, it is apparent that by mere inspection the notebook page does not establish either conception or an actual reduction to practice of the subject matter of the count. While the heading on **SSX** 32 refers to the enzyme, purified type IV collagenase, the underlying notes are directed to an inhibitor of the enzyme which is characterized as a 19 kDa protein. The subject matter of the first alternative of the count is directed to a protein of from about 20 to about 28 kilodaltons. Further, the **A2058** melanoma cell media utilized is not identified as fetal calf serum-free so the results obtained could not have ruled out the possibility of contamination from fetal calf serum. The second alternative for the count sets forth an amino acid sequence of 194 amino acids. The amino acid sequence on **SSX** 32 is only 34 amino acids long. Accordingly, the notebook page does not show either conception or an actual reduction to practice of the subject matter of the count.

Although we have found that Stetler-Stevenson et al. have failed to meet their burden of persuasion and failed to prove a conception of the subject matter of the count before Langley et al.'s effective filing date, we shall briefly address Stetler-Stevenson et al.'s alleged showing of "reasonable diligence." The time for which Stetler-Stevenson et al.'s were required to prove reasonable

diligence runs "from a time prior to conception by the other" up to a reduction to practice by Stetler-Stevenson et al., either actual or constructive. Assuming that Stetler-Stevenson et al. had proved prior conception and assuming further that Langley et al.'s date of conception was the date they filed their involved application in this proceeding, then the time period for which reasonable diligence must be shown is from just prior to May 19, 1989, up to Stetler-Stevenson et al.'s filing of their involved application in this proceeding, that is, July 17, 1989. Thus the time period is roughly two months.

Diligence, within the meaning of 35 U.S.C. § 102(g) is present when the inventors can show reasonably continuous activity during the critical period. Burns v. Curtis, 172 F.2d 588, 591, 80 USPQ 587, 589 (CCPA 1947). To satisfy the reasonable diligence requirement of 35 U.S.C. § 102(g), the party chargeable with diligence must account for the entire period during which diligence is required. Gould v. Schawlow, 363 F.2d 908, 918-19, 150 USPQ 634, 643 (CCPA 1966). Evidence of diligence during the critical period may be shown either by affirmative acts or acceptable excuses or reasons for failure of action. Hull v. Davenport, 90 F.2d at 105, 33 USPQ at 508. The inventors' testimony concerning diligence must be corroborated and the corroborative testimony must be specific as to dates and facts. Kendall v. Searles, 173 F.2d 986, 993, 81 USPQ 363, 368 (CCPA 1949). General allegations of continuing activity are

insufficient to show reasonable diligence. Wiesner v. Weigert, 666 F.2d 582, 588-89, 212 USPQ 721, 727 (CCPA 1981).

Stetler-Stevenson et al. have presented no evidence directed to specific acts on specific dates during the critical period. Stetler-Stevenson et al.'s position taken at page 11 of their brief that:

> There is no question that Stetler-Stevenson et al. were diligent in reducing the invention to practice. The project began on July 5, 1988 and reduced to practice by December 5, 1988, a mere five months period. The application for the invention was filed on March 21, 1989 to include more of the sequence of TIMP-2.

is not evidence but mere attorney argument. A similar statement on pages 27 and 28 of their brief under the heading "STETLER-STEVENSON WAS DILIGENT IN REDUCING THE INVENTION TO PRACTICE" is also unsupported argument. To the extent both statements are interspersed with references to the work of Dr.'s Stetler-Stevenson and Liotta, there is no corroboration of any of the inventors' alleged evidence of either conception or an actual reduction to practice.

Accordingly, we find no showing by Stetler-Stevenson et al. by a preponderance of the evidence that they conceived of an embodiment within the count including all the limitations of either alternative of the count prior to the senior party's constructive reduction to practice, that is, the filing of the senior party's involved application and their date of conception. We also find no evidence that Stetler-Stevenson et al. were diligent during the

critical time period from just prior to Langley et al.'s constructive conception, as evidenced by the filing of Langley et al.'s involved application, up to the filing of Stetler-Stevenson et al.'s involved application. We conclude, therefore, that Stetler-Stevenson et al. are not entitled to an award of priority based on their theory of prior conception coupled with reasonable diligence up to their constructive reduction to practice.

Stetler-Stevenson et al.'s alternative argument that they are entitled to an award of priority based on their alleged earlier actual reduction to practice before Langley et al.'s effective filing date of an embodiment within the first alternative of the count is not persuasive. According to their brief, Stetler-Stevenson et al. "reduced the invention to practice at the latest by December 5, 1988." See page 10 of the brief.

According to Stetler-Stevenson et al., Dr. Stetler-Stevenson isolated the Peak "**A**" material and had sequenced the first 10 (ten) amino acids of the **N**-terminus of the Peak "**A**" material on July 27, 1988. Nevertheless, the evidence on which Stetler-Stevenson et al. rely as proof of this allegation is the work of one of the named inventors. As such, the notebook requires corroboration independent of the inventors by a non-inventor. We have held, for reasons set forth fully above, Dr. Stetler-Stevenson's work, as reflected by his notebook, is not adequately corroborated. Further,

and more significantly, we also explained above that the work he allegedly performed on July 27, 1988, is not for an embodiment including every limitation of the first alternative of the count. Thus, it cannot serve as evidence of an actual reduction to practice.

Stetler-Stevenson et al.'s argument that the work performed by Dr. Stetler-Stevenson in November and December of 1988 using "bovine serum free conditioned media of **A2058** melanoma cells" (see page 13 of the brief) culminated in the sequencing of 40 amino acids of the **N**-terminus of TIMP-2 on December 8, 1988, is an apparent reference to **SSX** 6 at page 109. Therein the following handwritten information is set forth:

> Material obtained from peak # 1 RP-HPLC 12-5-88 was sequenced without prior enzyme treatment to obtain amino terminal amino acid sequence.
>
> Sequence Obtained:
>
> 12345678910111213141516171819 20 30 40
> **CSCSPVHPQQ A F C N A D V V I RAKAVSEKEYDSGNPIYGNNI**
>
> Amino acid searches showed 80% identity in a 35 aa overlap with bovine collagenase inhibitor 71.4 to 63.3% identity in a 30 aa overlap with human collagenase inhibitor (TIMP-1)
>
> The source for this material is human **A2058** melanoma cells. Thus this material represents human tumor cell collagenase inhibitor MCIP melanoma collagenase inhibitor protein (or tumor cell collagenase inhibitor TCCI)

We have omitted reference to some other handwritten notes, date stamps and initialing on page 109 which are not relevant to our inquiry.

The reference on page 109 to work performed on 12-5-88 is an apparent reference to page 105 of **SSX** 6 wherein the following handwritten information is set forth:

> 400 µl type IV collagenase prep 11-30-88 was injected into RP-HPLC system. Material eluting under peak # 1 and peak # 2 was collected. Acetonitrile was evaporated under a N^2 stream and the sample was neutralized by addition of 1M Tris. Material from peak # 1 was submitted for amino acid sequencing. See page 109.

The only evidence of any work in Dr. Stetler-Stevenson's notebook (**SSX** 6) performed on November 30, 1988, is a machine printout from a "Data File" denominated as "HPLC0017.D01" which shows along an X-Y axis two unlabeled peaks, one at about 27 minutes and one at about 30 minutes. Thus, we are unable to identify the nature of the "type IV collagenase prep." which was eluted and collected on December 5, 1988.

We find that the alleged actual reduction to practice on December 8, 1988, has not been established to be for an embodiment including <u>every</u> limitation of the first alternative of the count. At best, we understand from the entries in his notebook that Dr. Stetler-Stevenson had: collected a sample described only as "type IV collagenase prep"; subjected that sample to reverse phase (RP) HPLC[10]; obtained at least two fractions from the sample represented

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[10] Stetler-Stevenson et al. have not favored the record with an explanation of the various and numerous abbreviations and acronyms used in the various notebooks on which they rely. Thus, we have been required to speculate as to their meaning as set forth in our opinion based on our best informed understanding of

by "peak # 1" and "peak # 2"; evaporated a solvent (acetonitrile) from the samples; treated the samples with a buffer (Tris); and, submitted the "peak # 1" material for amino acid sequencing. Nothing in **SSX** 6 at page 109 shows that Dr. Stetler-Stevenson had obtained a purified and isolated human protein which is a tissue inhibitor of metalloproteinases and which (1) has a molecular weight of from about 20 kDa to about 28 kDa; (2) forms a complex with the latent form of the 72-kDa type IV collagenase; and, (3) has an **N**-terminal amino acid sequence **SPVHPQQAFCNADVVIRAKAVS**. Further, for the reasons set forth above with respect to the alleged corroboration of the inventors' notebooks and testimony, no non-inventor has corroborated the evidence which Stetler-Stevenson et al. have proffered as evidence of an actual reduction to practice of the subject matter of the count. Stetler-Stevenson et al. have, therefore, failed to prove by a preponderance of the evidence that they actually reduced to practice an embodiment including every limitation of the first alternative of the count. Accordingly, we find that Stetler-Stevenson et al. are not entitled to an award of priority with respect to the subject matter of the count.

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the research in which Stetler-Stevenson et al. was engaged.

JUDGMENT

Having considered all the evidence placed before us and decided all the issues properly raised, it is now appropriate to render final judgment in this interference. Accordingly, pursuant to our authority under 37 C.F.R. § 1.658(a), and in view of our holding that Goldberg and Stetler-Stevenson et al. have failed to meet their burden of persuasion, we enter the following judgment.

Judgment as to the subject matter of Count 3 in this interference is entered against Gregory Goldberg, a junior party. Gregory Goldberg, a junior party, is not entitled to a patent containing claims 1 and 2 in his involved application Serial Number 07/358,043 in this interference and designated as corresponding to Count 3.

Judgment as to the subject matter of Count 3 in this interference is entered against William G. Stetler-Stevenson, Lance A. Liotta and Henry C. Krutzsch, a junior party. William G. Stetler-Stevenson, Lance A. Liotta and Henry C. Krutzsch, a junior party, are not entitled to a patent containing claims 1, 9, 11 and 23 through 25 in their involved application Serial Number 07/380,431 in this interference and designated as corresponding to Count 3.

Judgment as to the subject matter of Count 3 is awarded to Keith E. Langley, Yves A. Declerk and James Thomas Boone, the senior party. On this record, as the first inventors of the subject matter

of Count 3, Keith E. Langley, Yves A. Declerk and James Thomas Boone are entitled to a patent containing claims 1 through 4, 6, 7, 9 through 11, 31, 32, 37 and 40 through 43 in their involved application Serial Number 07/355,027 and designated as corresponding to Count 3.

ANDREW H. METZ
Administrative Patent Judge)

TEDDY S. GRON
Administrative Patent Judge) BOARD OF PATENT APPEALS AND INTERFERENCES

ADRIENE LEPIANE HANLON
Administrative Patent Judge)

AHM/gjh

Attorney(s) for Goldberg:

Scott J. Meyer, Esq.
Monsanto Company - 04B
800 North Lindberg Blvd.
St. Louis, Missouri 63167

Attorney(s) for Langley et al.:

Paul Barker, Esq.
Finnegan, Henderson, Farabow, Garrett
& Dunner, L.L.P.
700 Hansen Way
Palo Alto, CA 94304

Attorney(s) for Stetler-Stevenson et al.:

William S. Feiler, Esq.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154-0053